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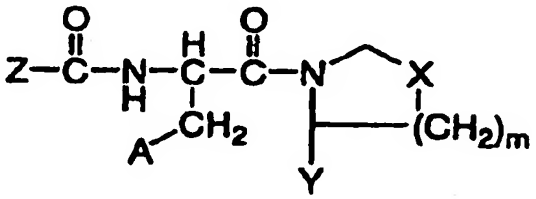
(54) NOVEL PEPTIDE DERIVATIVES HAVING THIAZOLYL-ALANINE RESIDUE

(57) The compounds having superior activity to known TRH and its derivatives in view of the activation of the central nervous system, for example, sustained acetylcholine releasing action, anti-reserpine action and locomotor increment activity was provided.

A peptide derivative of the formula (I):



(I)

, its pharmaceutically acceptable salt, or hydrate thereof.

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Description

Technical Field

[0001] This invention relates to a new peptide derivative having the residue of 3-(4-thiazolyl or 5-thiazolyl)-alanine and having an effect of activating the central nervous system. The compound of this invention is useful as a medicament.

Background Art

[0002] The compound of this invention is derived from L-pyroglutamyl-L-histidyl-L-prolineamide (p-Glu-His-Pro-NH_2), known as TRH (thyrotropin releasing hormone) isolated from hypothalamus.

[0003] TRH is a hormone consisting of 3 amino acid residues isolated from hypothalamus, and seems to show the activities through a TRH receptor. It is known not only to promote the secretion of TSH (thyroid stimulating hormone) and prolactin, but also to have the following activity; brain nervous system activation such as motor stimulating activity etc., sympathetic activity such as blood pressure elevation, respiratory stimulation, etc., spinal activity such as spinal motor nerve stimulation etc., central nervous activity such as antidepression etc., and peripheral activity such as gastrin secretion suppression, glucagon secretion stimulation, etc. Because TRH has such various activity, it has been investigated on the clinical use, and is being used as an intravenous injection for treating spinocerebellar degeneration for purposes of improvement of motility disturbance and cognitive disturbance accompanied by brain functional disturbance (Sofue, Kanazawa, Ogawa, "Neuropeptide" '91, Medicalreview).

[0004] However, there are various problems barring the clinical application of TRH. Typical ones are described below:

1) TRH shows very short half-time in blood and is required to be administered frequently, because it is digested by enzymes such as pyroglutamyl peptidase, TRH amidase, etc. in a living body.
2) Excessive secretion of TSH is caused by repeated administration of TRH due to the activity of stimulating secretion of TSH.
3) A slight mount of TRH is transferred into brain by peripheral administration because of its low hydrophobicity.

[0005] In order to solve the above problems concerning TRH, the development of TRH derivatives which have more potent activity than TRH in view of activation of the central nervous system (for example, awaking stimulation, anti-reserpine activity (hyperthermia), locomotor increment, spinal reflex increase, dopamine action potentiation, anti-anesthetic action, etc.) and have long duration of action has been attempted. Such compounds reported at the present time are illustrated below.

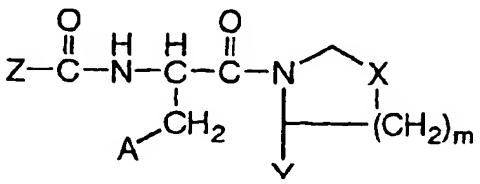
[0006] For example, 1-methyl-L-4,5-dihydroorotyl-L-hystidyl-L-prolineamide (JP-B 2-36574), 2,3,4,5-tetrahydro-2-oxo-L-5-furancarbonyl-L-histidyl-L-prolineamide (JP-A 52-116465), (1S, 2R)-2-methyl-4-oxocyclopentylcarbonyl-L-histidyl-L-prolineamide (JP-B-3-236397), orotyl-L-histydyl-L-prolineamide (JP-B 59-36612), TRH-SR (Eur. J. Pharmacol., 271, 357 (1994)), etc. are known

[0007] However, the above TRH derivatives do not have enough continuous action. Additionally, intravenous injection of these compounds makes it difficult to improve the compliance to the periodical administration of them and QOL (Quality of Life) of patients having the motor disturbance.

Disclosure of Invention

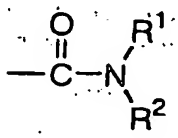
[0008] In the above situation, the inventors of the present invention found the compounds having superior activity known TRH and its derivatives in view of the activation of the central nervous system, for example, sustained acetylcholine releasing action, anti-reserpine action and locomotor increment activity. The present invention relates to

a) A peptide derivative of the formula (I):

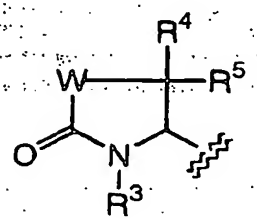


(I)

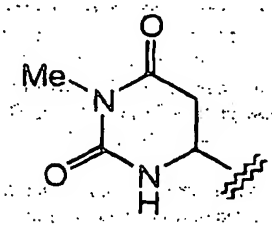
wherein A is 4-thiazolyl or 5-thiazolyl wherein the nitrogen in the thiazolyl ring may be quarternary nitrogen which is formed with optionally substituted alkyl or alkenyl, X is a bond, oxygen, or sulfur, m is an integer of 0 to 4, Y is optionally substituted alkyl, optionally substituted carboxy, cyano, or the substituent represented by the formula:



wherein R^1 and R^2 are independently hydrogen or optionally substituted alkyl, or R^1 and R^2 taken together with may form a non-aromatic heterocyclic ring the adjacent nitrogen which may contain oxygen, nitrogen, or sulfur and may be substituted, Z is the substituent represented by the formula:

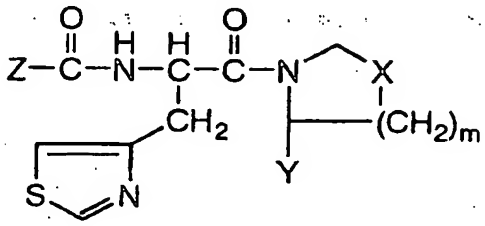


wherein R^3 is hydrogen, optionally substituted alkyl, optionally substituted carboxy, or optionally substituted acyl, R^4 and R^5 are each independently hydrogen or optionally substituted alkyl, and W is $-(CH_2)n-$ wherein n is 0, 1, 2, or 3, oxygen, sulfur, or optionally substituted imino, or the substituent represented by the formula:



its pharmaceutically acceptable salt, or hydrate thereof.

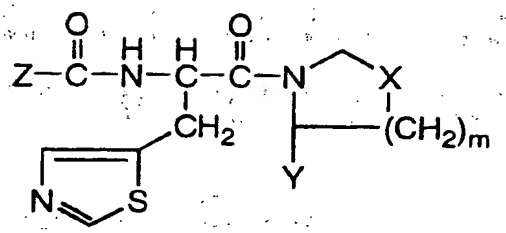
b) A peptide derivative of the formula (II):



(II)

wherein X, Y, Z, and m are as defined above, and the nitrogen in the thiazolyl ring may be quarternary nitrogen which is formed with optionally substituted alkyl or alkenyl, its pharmaceutically acceptable salt, or hydrate thereof.

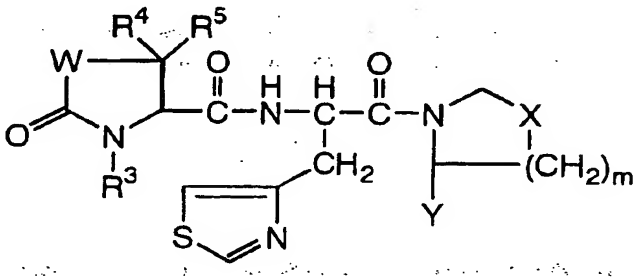
c) A peptide derivative of the formula (III):



(III)

wherein X, Y, Z, and m are as defined above, and the nitrogen in the thiazolyl ring may be quarternary nitrogen which is formed with optionally substituted alkyl or alkenyl, its pharmaceutically acceptable salt, or hydrate thereof.

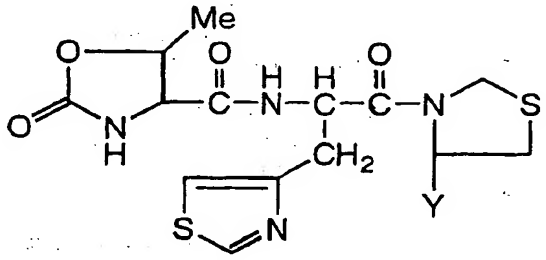
d) A peptide derivative of the formula (IV):



(IV)

wherein W, X, Y, m, R^3, R^4, and R^5 are as defined above, its pharmaceutically acceptable salt, or hydrate thereof.

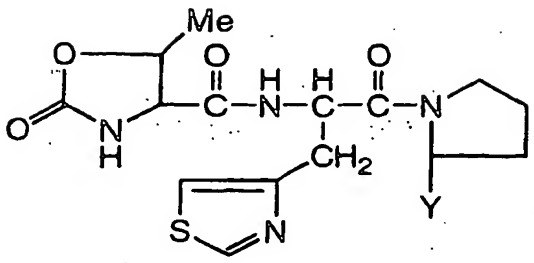
e) A peptide derivative of the formula (V):



(V)

wherein Y is as defined above, its pharmaceutically acceptable salt, or hydrate thereof.

f) A peptide derivative of the formula (VI):



(VI)

wherein Y is as defined above, its pharmaceutically acceptable salt, or hydrate thereof.

g) A peptide derivative of any one of a) to d) wherein m is 1 or 2, provided that X is not a bond when m is 1, its pharmaceutically acceptable salt, or hydrate thereof.

h) A peptide derivative of any one of a) to d) wherein m is 1 and Y is optionally substituted alkyl, optionally substituted carboxy, or optionally substituted carbamoyl, its pharmaceutically acceptable salt, or hydrate thereof.

i) A peptide derivative of any one of a) to d) wherein m is 2 or 3 and Y is optionally substituted alkyl, optionally substituted carboxy, or optionally substituted carbamoyl, its pharmaceutically acceptable salt, or hydrate thereof.

j) A pharmaceutical composition which contains any one of the compounds a) to i) as an active ingredient.

k) A composition for activating the central nervous system which contains any one of the compounds a) to i) as an active ingredient.

l) A TRH derivative having such effect that the ratio represented by the blood glucose level of the active substance-administered group / the blood glucose level of the physiological saline-administered group is 0.7 to 1.3 in the rat to which an effective amount of it for exhibiting the main activity is intravenously administered.

[0009] All of the compounds represented by the above formula have superior activity of activating the central nervous system. Specifically, the compounds having the substituents shown below in the formula (IV) are preferable.

1) A peptide derivative wherein W is oxygen, X is oxygen or sulfur, Y is carbamoyl or optionally substituted alkyl, m is 1, R^3 is hydrogen, R^4 is optionally substituted alkyl, and R^5 is hydrogen, its pharmaceutically acceptable salt, or hydrate thereof.

2) A peptide derivative wherein W is oxygen, X is a bond, Y is carbamoyl or optionally substituted alkyl, m is 2, R^3 is hydrogen, R^4 is optionally substituted alkyl, and R^5 is hydrogen, its pharmaceutically acceptable salt, or hydrate thereof.

[0010] As further preferable compounds, the compounds having the substituents shown below in the formula (IV) are exemplified.

1') A peptide derivative wherein W is oxygen, X is oxygen or sulfur, Y is carbamoyl or alkyl, m is 1, R^3 is hydrogen, R^4 is alkyl, and R^5 is hydrogen, its pharmaceutically acceptable salt, or hydrate thereof.

2') A peptide derivative wherein W is oxygen, X is a bond, Y is carbamoyl or alkyl, m is 2, R^3 is hydrogen, R^4 is alkyl, and R^5 is hydrogen, its pharmaceutically acceptable salt, or hydrate thereof.

[0011] As further preferable compounds, the compounds having the substituents shown below in the formula (IV) are exemplified.

1") A peptide derivative wherein W is oxygen, X is sulfur, Y is carbamoyl or C_1-C_6 straight or branched chain alkyl, m is 1, R^3 is hydrogen, R^4 is C_1-C_3 straight or branched chain alkyl, and R^5 is hydrogen, its pharmaceutically acceptable salt, or hydrate thereof.

2") A peptide derivative wherein W is oxygen, X is a bond, Y is carbamoyl or C_1-C_6 straight or branched chain alkyl, m is 2, R^3 is hydrogen, R^4 is C_1-C_3 straight or branched chain alkyl, and R^5 is hydrogen, its pharmaceutically acceptable salt, or hydrate thereof.

[0012] As a preferable configuration, the configuration represented by the formula (IV') for the formula (IV) (when one of R^4 and R^5 is hydrogen, the configuration shows the other one than shown in the formula)

[0013] The term "halogen" herein used means fluoro, chloro, bromo, and iodo.

[0014] The term "alkyl" herein used includes C_1-C_6 straight or branched chain alkyl and C_3-C_6 cyclic alkyl. Preferably, C_1-C_6 straight or branched chain alkyl is exemplified. Further preferably, C_1-C_3 straight or branched chain alkyl is exemplified. Examples of alkyl are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, and the like.

[0015] The term "alkenyl" herein used includes C_2-C_8 straight or branched chain alkenyl. Preferably, C_3-C_6 straight or branched chain alkenyl is exemplified. Further preferably, C_2-C_5 straight or branched chain alkenyl is exemplified. Examples of alkenyl are n-propenyl, n-butenyl, n-hexenyl, and the like.

[0016] The term "aryl" herein used includes monocyclic or condensed ring aromatic hydrocarbons. Preferably, monocyclic aromatic hydrocarbons are exemplified. Examples of aryl are phenyl, naphthyl, and the like.

[0017] The term "heteroaryl" includes a 5 to 6 membered aromatic heterocyclic group which contains one or more hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in the ring, may be fused with a carbocyclic ring or an other heterocyclic ring, and may be substituted at any possible position. Examples of the heteroaryl are pyrrolyl (e.g., 1-pyrrolyl), indolyl (e.g., 2-indolyl), carbazolyl (e.g., 3-carbazolyl), imidazolyl (e.g., 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl), benzimidazolyl (e.g., 2-benzimidazolyl), indazolyl (e.g., 3-indazolyl), indolizinyl (e.g., 6-indolizinyl), pyridyl (e.g., 4-pyridyl), quinolyl (e.g., 5-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), acridinyl (e.g., 1-acridinyl), phenanthridinyl (e.g., 2-phenanthridinyl), pyridazinyl (e.g., 3-pyridazinyl), pyrimidinyl (e.g., 4-pyrimidinyl), pyrazinyl (e.g., 2-pyrazinyl), cinnolinyl (e.g., 3-cinnolinyl), phthalazinyl (e.g., 2-phthalazinyl), quinazolinyl (e.g., 2-quinazolinyl), isoxazolyl (e.g., 3-isoxazolyl), benzisoxazolyl (e.g., 3-benzisoxazolyl), oxazolyl (e.g., 2-oxazolyl), benzoxazolyl (e.g., 2-benzoxazolyl) benzoxadiazolyl (e.g., 4-benzoxadiazolyl), isothiazolyl (e.g., 3-isothiazolyl), benzisothiazolyl (e.g., 2-benzisothiazolyl), thiazolyl (e.g., 2-thiazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), fury] (e.g., 3-furyl), benzofuryl (e.g., 3-benzofuryl), thienyl (e.g., 2-thienyl), benzothienyl (e.g., 2-benzothienyl), tetrazolyl, and the like.

[0018] The term "non-aromatic heterocyclic group" herein used means a 5 to 7 membered non-aromatic heterocyclic group which contains one or more hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in the ring, and may bind at any possible position. Examples of the non-aromatic heterocyclic group are morpholino, piperidino, 1-pyrrolidinyl, 2-pyrroline-3-yl, and the like.

[0019] The term "acyl" herein used includes alkanoyl of which alkyl part is the above mentioned "alkyl" and aroyl of which aryl part is the above mentioned "aryl". Examples of acyl are acetyl, benzoyl, and the like.

[0020] The term "alkyloxy" herein used includes alkyloxy of which alkyl part is the above mentioned "optionally substituted alkyl". Examples of alkyloxy are methyloxy, ethyloxy, n-propyloxy, iso-propyloxy, n-butyloxy, iso-butyloxy, sec-butyloxy, tert-butyloxy, and the like.

[0021] The term "optionally substituted alkyl" for R^1 and R^2 herein used includes the above mentioned "alkyl" which is optionally substituted at any possible position with one or more substituents, for example, hydroxy, alkyloxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl), halogen (e.g., fluoro, chloro, bromo, and iodo), carboxy, carbamoyl, C_1-C_{20} alkyloxycarbonyl (e.g., methoxycarbonyl, iso-propyloxycarbonyl, tetradecanyloxycarbonyl, and pentadecanyloxycarbonyl), aryloxycarbonyl (e.g., phenyloxycarbonyl), nitro cyano, SO_pR^A (p is an integer of 1 to 3, and R^A is hydrogen or alkyl), $PO(OH)_2$ or PO(O)OH which is optionally substituted with alkyl substituted or unsubstituted amino (e.g., methylamino, dimethylamino, and carbamoylamino), optionally substituted aryl (e.g., phenyl and tolyl), optionally substituted heteroaryl, an optionally substituted non-aromatic-heterocyclic group aryloxy, acyloxy, acyloxycarbonyl, alkylcarbonyl, arylcarbonyl, non-aromatic heterocyclic carbonyl, hydrazino, hydroxyamino, alkyloxyamino, and formyl. Examples of optionally substituted alkyl are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, benzyl, iso-propyloxycarbonylmethyl, tetradecanyloxycarbonylmethyl, pentadecanyloxycarbonylmrthyl, and the like. As the preferred substituent, C_1-C_{20} alkyloxycarbonyl and phenyl are exemplified.

[0022] The term "optionally substituted alkyl" for Y, R^3, R^4, and R^5 herein used includes the above mentioned "alkyl" which is optionally substituted at any possible position with one or more substituents, for example, hydroxy, alkyloxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl), halogen (e.g., fluoro, chloro, bromo, and iodo), carboxy, carbamoyl, alkyloxycarbonyl (e.g., methoxycarbonyl and ethoxycarbonyl), aryloxycarbonyl (e.g., phenyloxycarbonyl), nitro, cyano, SO_pR^A (p is an integer of 1 to 3, and R^A is hydrogen or alkyl), $PO(OH)_2$ or PO(O)OH which is optionally substituted with alkyl, substituted or unsubstituted amino (e.g., methylamino, dimethylamino, and carbamoylamino), optionally substituted aryl (e.g., phenyl and tolyl), optionally substituted heteroaryl, an optionally substituted non-aromatic-heterocyclic group, aryloxy, acyloxy, acyloxycarbonyl, alkylcarbonyl, non-aromatic heterocyclic carbonyl, heterocyclic imino, hydrazino, hydroxyamino, alkyloxyamino, and formyl. For example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, benzyl, hydroxymethyl, tert-butylcarbonyloxymethyl, morpholinomethyl, piperidinomethyl, N-methyl-1-piperazinylmethyl, ethylcarbonylmethyl, morpholinocarbonylmethyl, acetyloxymethyl, and the like are exemplified. As a preferable substituent, phenyl, hydroxy, alkylcarbonyloxy, morpholino, piperidino, N-alkyl-substituted piperazinyl, alkylcarbonyl, morpholinocarbonyl, acyloxy are exemplified.

[0023] The term "optionally substituted alkyl" for nitrogen in the thiazolyl ring herein used includes C_1-C_3 straight or branched chain alkyl which is optionally substituted with phenyl optionally substituted with halogen or alkyl. For example, methyl, ethyl n-propyl, n-butyl, benzyl, 4-methylbenzyl are exemplified.

[0024] The terms "optionally substituted aryl", "optionally substituted heteroaryl", and "an optionally substituted non-aromatic heterocyclic group" herein used include the above mentioned "aryl", "heteroaryl", and "a non-aromatic heterocyclic group", respectively, which are optionally substituted with one or more substituents, for example, hydroxy, alkyloxy (e.g: ,methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), halogen (e.g., fluoro, chloro, bromo, and iodo), carboxy, alkyloxycarbonyl (e.g., methoxycarbonyl and ethoxycarbonyl), nitro, cyano, haloalkyl (e.g., trifluoromethyl), aryloxy (e.g., phenyloxy), substituted or unsubstituted amino (e.g., methylamino, dimethylamino, diethylamino, and benzylideneamino), guanizino, alkyl (e.g., methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, tert-pentyl, cyclopropyl, cyclobutyl, and cyclopentyl), alkenyl (e.g., vinyl and propenyl), alkynyl (e.g., ethynyl and phenylethynyl), alkanoyl (e.g., formyl, acetyl and propionyl), acyloxy (e.g., acetyloxy) acylamino, alkylsulfonyl (e.g., methylsulfonyl), phenyl, benzyl, an azo group (e.g., phenylazo), optionally substituted heteroaryl (e.g., 3-pyridyl), optionally substituted ureido (e.g., ureido and phenylureido), and the like.

[0025] The substituents for "optionally substituted carboxy" of Y are, for example, straight or branched chain C_1-C_{20} alkyl, cyclic C_3-C_8 alkyl, and aryl. Further, these alkyl and aryl are optionally substituted with one or more substituents which are exemplified as those for the above "optionally substituted alkyl" and "optionally substituted aryl". Examples of the "optionally substituted carboxy" are carboxy, alkyloxycarbonyl and aryloxycarbonyl, for example, methoxycarbonyl, iso-propyloxycarbonyl, hexyloxycarbonyl, decyloxycarbonyl, phenyloxycarbonyl, tetradecyloxycarbonyl, icosanyloxycarbonyl, phenoxymethylcarbonyl, benzyloxycarbonyl, tolyloxycarbonyl, and the like. As a preferable substituent, straight or branched chain C_1-C_{20} alkyl and benzyl are exemplified.

[0026] The substituents for "optionally substituted carbamoyl" of Y are, for example, straight or branched chain C_1-C_6 alkyl (e.g., methyl, ethyl n-propyl, and iso-propyl). Further, this alkyl is optionally substituted with one or more substituents which are exemplified as those for the above "optionally substituted alkyl". Examples of the "optionally substituted carbamoyl" are carbamoyl, methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, methylethylcarbamoyl, benzylcarbamoyl, iso-propyloxycarbonylmethylcarbamoyl, tetradecanyloxycarbonylmethylcarbamoyl, benzyloxycarbonylmethylcarbamoyl, acetyloxymethylcarbamoyl, acetylcarbamoyl, and the like. As a preferable substituent, C_1-C_{20} alkyloxycarbonylalkyl and acyloxyalkyl are exemplified.

[0027] The substituents for "optionally substituted carboxy" of R^3 are, for example, the above mentioned "optionally substituted alkyl" and "optionally substituted aryl". Examples of the "optionally substituted carboxy" are carboxy, alkyloxycarbonyl, and aryloxycarbonyl, for example, methoxycarbonyl, ethoxycarbonyl, phenoxycarbonyl, phenyloxymethylcarbonyl, tolyloxycarbonyl, and the like.

[0028] The term "optionally substituted acyl" herein used includes alkanoyl of which alkyl part is the above mentioned "optionally substituted alkyl" and aroyl of which aryl part is the above mentioned "optionally substituted aryl". Examples of the "optionally substituted acyl" are toluoyl and the like.

[0029] The term "optionally substituted imino" herein used includes the imino which is optionally substituted with the above mentioned "optionally substituted lower alkyl", "optionally substituted aryl", alkyloxycarbonyl, and the like.

Brief Description of Drawings

[0030]

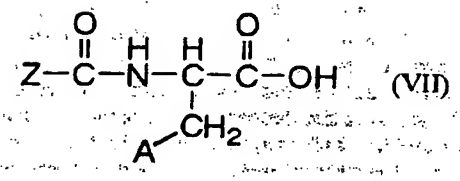
Figure 1 shows the effect of releasing acetylcholine in cerebral cortex when the test compound is orally administered to rats (the horizontal axis shows time course and the vertical axis shows a concentration of acetylcholine in cerebral cortex.).

Figure 2 shows the transition of the blood glucose level by intravenous injection to rats (the horizontal axis shows time course and the vertical axis shows the blood glucose level).

Best Mode for Carrying Out the Invention

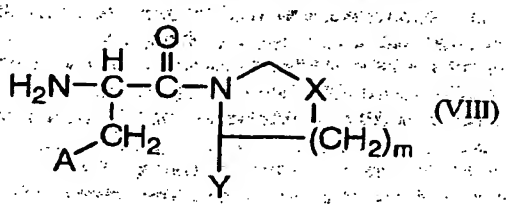
[0031] The compounds of this invention are able to be synthesized by means of the following methods A and B as a usual method of the peptide synthesis. The substituents, for example, Y and the like are able to be introduced by alkylation, acylation, esterification, etc. after the tripeptide was synthesized in the same manner as the method A or B.

[0032] The compound represented by the formula (VII):



(VII)

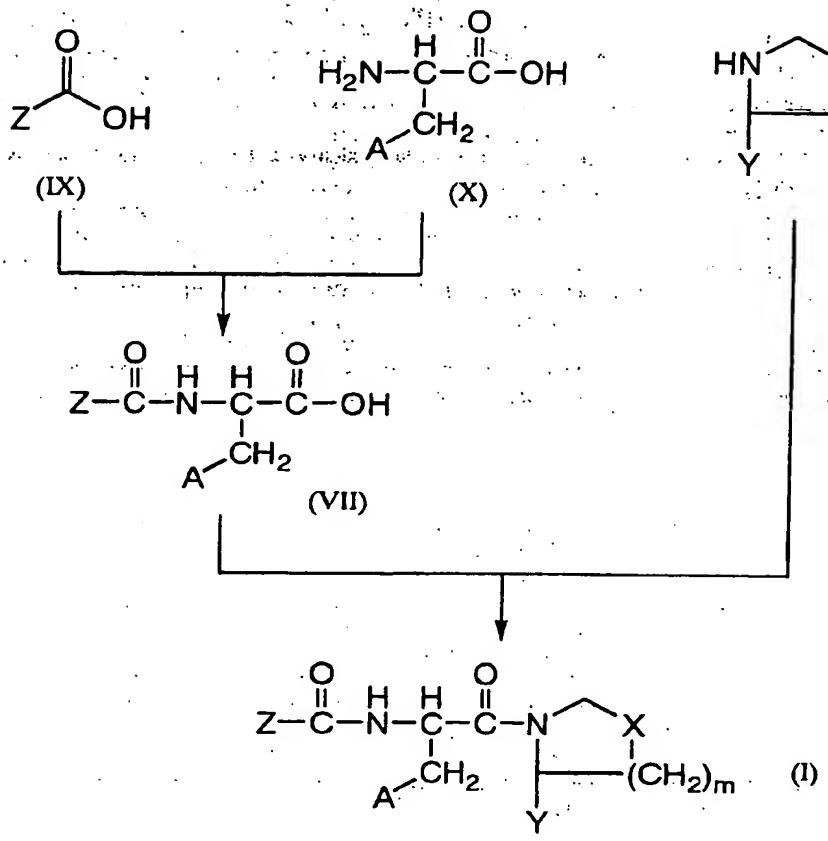
wherein A and Z are as defined above, and the compound of the formula (VIII):



(VIII)

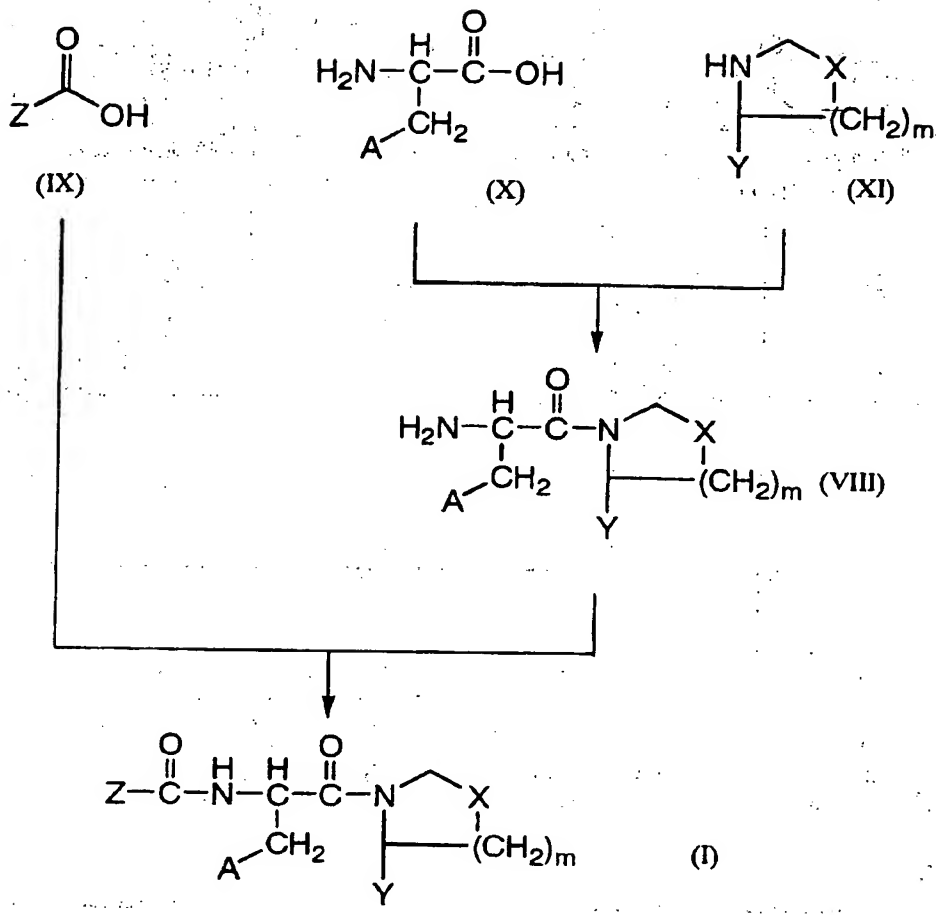
wherein A, X, Y, and m are as defined above, which are intermediates for the methods A and B, are novel.

(Method A)



wherein A, X, Y, Z, and m are as defined above.

(Method B)



wherein A, X, Y, Z, and m are as defined above.

[0033] The methods A and B are to obtain the aimed compound of tripeptide (I) using the amino acid derivatives represented by the formulas (IX), (X), and (XI) as a starting material. In the method A the compound (IX) is reacted with the compound (X) to give the compound (VII), which is further reacted with the compound (XI). In the method B the compound (X) is reacted with the compound (XI) to give the compound (VIII), which is then reacted with the compound (IX). Each reaction is carried out in accordance with a usual peptide synthetic reaction for example, the method described in "The Peptide", vol. 1, "Peptide Synthesis", Nobuo Izumiya, Maruzen and the like.

[0034] As a usual peptide synthetic reaction, exemplified are the method of using a condensing agent such as N, N-dicyclohexylcarbodiimide (DCC) and the like, the azide method, the acid chloride method, the acid anhydride method, the activated ester method, and the like. When the starting material has a substituent interfering this peptide synthetic reaction, for example, amino, carboxy, hydroxy, etc., the substituent can previously be protected in accordance with the method of " Protective Groups in Organic Synthesis" Theodora W. Green (John Wiley & Sons), and then deprotected at an appropriate step.

[0035] Examples of an amino protective group are t-butyloxycarbonyl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, phthaloyl, trifluoroacetyl, and the like.

[0036] Examples of a carboxy protective group are esters such as methyl ester, ethyl ester, benzyl ester, t-butyl ester, 2-(trimethylsilyl)ethyl ester, etc.

[0037] As the method to activate the carboxy concerning the reactions of the compounds (VII), (IX), and (X), the following methods are exemplified; 1) the method to give activated esters such as N-hydroxysuccinimide ester, N-hydroxybenzotriazole ester, p-nitrophenol ester, and the like, 2) the method to give acid chlorides using chlorination agents such as phosphorus oxychloride, phosphorous trichloride, thionyl chloride, oxalyl chloride, and the like, 3) the method to give asides, 4) the method to give acid anhydrides. These methods are able to be carried out in the presence or absence of a deoxidizer in an appropriate solvent such as N, N-dimethylformamide, acetonitrile, tetrahydrofuran, methylene chloride, and the like at -50 °C to reflux.

[0038] The active derivatives of carboxylic acids which are produced by the above methods are isolated and are able to be reacted with the compounds (VIII), (X), and (XI) having an amino group concerning this reaction. Without isolating the active derivatives of carboxylic acids in the above methods, the compounds (VIII), (X), and (XI) having an amino group concerning this reaction may be added to the reaction solution of the above methods. 1-Hydroxybenzotriazole may be added to the reaction mixture to expedite these reactions.

[0039] In this way, the compounds of this invention are able to be synthesized from amino acid derivatives of the compounds (IX), (X), and (XI) by two peptide synthetic reactions. The starting material of the amino acid derivatives are able to be obtained as known natural compounds and to be synthesized from them easily. The compound (IX) is able to be synthesized in accordance with the methods described in J. Med. Chem., 33, 2130 (1990), Int. J. Peptide Protein Res., 14, 216 (1979), Chem. Lett., 1171 (1982), and Tetrahedron Lett., 36, 6569 (1995). The compound (X) is able to be synthesized in accordance with the methods described in Synthetic Commun., 20, 3507 (1990) and EP 417454. The compound (XI) is able to be synthesized in accordance with the method described in J. Med. Chem., 24, 692 (1981).

[0040] The term "the compounds of this invention" herein used includes pharmaceutically acceptable salts or hydrates of the compounds. For example, salts with alkali metals (e.g., lithium, sodium, and potassium), alkaline earth metals (e.g., magnesium and calcium), ammonium, organic bases, amino acids, mineral acids (e.g., hydrochloric acid, hydrobromic acid, phosphoric acid, and sulfuric acid), or organic acids (e.g., acetic acid, citric acid, maleic acid, fumaric acid, benzenesulfonic acid, and p-toluenesulfonic acid) and hydrates of them are exemplified. These salts and hydrates can be formed by the usual method.

[0041] The compound of this invention is TRH derivative of which the histidine residue is converted into the residue of 3-(4-thiazolyl)alanine or 3-(5-thiazolyl)alanine and has strong, continuous, and selective action on the central nervous system. Administration of TRH and conventional TRH derivatives acutely raises up the blood glucose level and acutely let it fall down by the rebound, which are not observed in the compound of this invention. This fact may lead to the less side effect.

[0042] Since the compound of this invention has superior hyperthermia and locomotor increment effects caused by activation of the neurones such as dopamine system, norepinephrine system, and acetylcholine system in brain, it is useful for treatment of disorders accompanied with dysfunction of these nervous systems. Especially as it remarkably activates the acetylcholine neurone system in cerebral cortex, it may be useful as a therapeutic agent of disorders such as motor disturbance, disturbance of consciousness, senile dementia, sopor, decline of concentration, speech dysfunction, and the like accompanied with the dysfunction of the acetylcholine neurone.

[0043] When the compound of this invention is administered to a person for treatment or prevention of the above diseases, it can be administered by oral administration such as powder, granules, tablets, capsules, pilulae, and liquid medicine, or by parenteral administration such as injections, suppository, percutaneous formulations, insufflation, or the like. An effective amount of the compound of this invention is formulated by being mixed with medicinal admixture such as excipient, binder penetrant, disintegrators, lubricant, and the like if necessary. When parenteral injection is prepared, the compound of this invention and an appropriate carrier are sterilized to prepare it.

[0044] An appropriate dosage varies with the conditions of the patients, an administration route, their age, and their body weight. In the case of oral administration to adult, a dosage can generally be between 0.1 - 100 mg/kg/day, preferably 1 - 20 mg/kg/day.

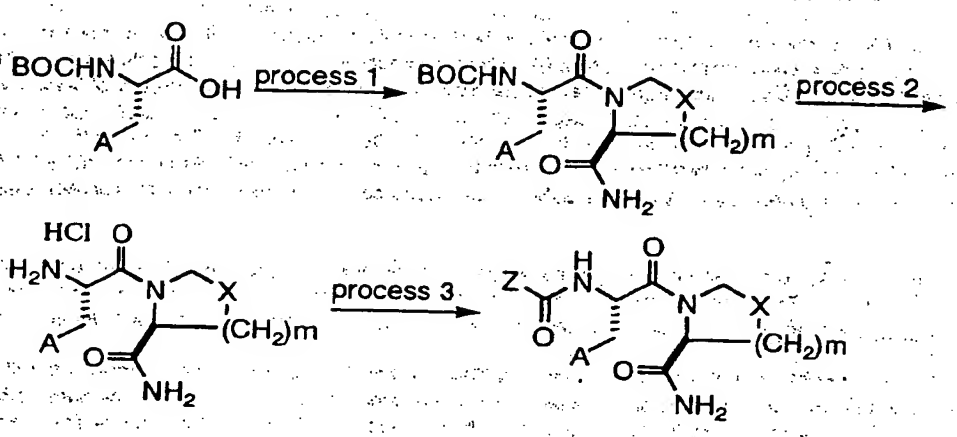
[0045] The following examples are provided to further illustrate the present invention and are not to be construed as limiting the scope thereof.

[0046] Abbreviations described below are used in the following examples.

c- : cyclo
Me : methyl
Et : ethyl
Pr : propyl
Bu : butyl
Pen : pentyl
Hex : hexyl
Ph : phenyl
Ac : acetyl

BOC : tert-butyloxycarbonyl
Bzl : benzyl
Cbz : benzyloxycarbonyl
p-TsOH : p-toluenesulfonic acid
DCC: N, N-dicyclohexylcarbodiimide
HOBT: 1-hydroxybezotriazole

Example



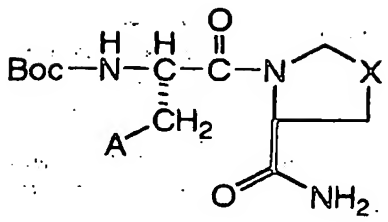
Example 1- process 1

Preparation of N-(tert-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl-L-prolineamide (1)

[0047] N-(tert-butyloxycarbonyl)-3-(4-thiazolyl)-L-alanine (8.17 g, 30 mmol) which was synthesized in accordance with the method described in the literature (Synthetic Commun., 20, 3507 (1990)) and L-prolineamide (3.42 g, 30 mmol) were dissolved in N, N-dimethylformamide (100 ml). To this solution was added the solution of dicyclohexylcarbodiimide (DCC, 6.81 g, 33 mmol) in N,N-dimethylformamide (10 ml) and 1-hydroxybenzotriazole (405 mg, 3 mmol) under ice-cooling with stirring and the resulting mixture was stirred overnight at room temperature. To the reaction mixture was added ethyl acetate (200 ml) and the precipitation which appeared was filtered off. The filtrate was concentrated in-vacuo. The residue (15.98 g) was subjected to silica gel column chromatography (chloroform : methanol = 98:2 to 97:3) to give the compound (1) (10.01 g, 90.6 %).

The compounds (2) and (3) were synthesized in a manner similar to that described in the above method. The results were shown in Table 1.

Table 1



Example No.	Compound No.	A	X	$[\alpha]_D$	melting point (°C)	NMR
1-1	1	4-thiazolyl	CH_2	-57.1° (c=1.004, $CHCl_3$, 23.5 °C)		(CD_3OD) 1.38 (9H, s), 1.8-2.3 (4H, m), 3.19 (2H, ddd), 3.47 (1H, m), 3.76 (1H, m), 4.44 (1H, dd), 4.68 (1H, dd, J=6.2, 7.4 Hz), 7.33, 7.40 (total 1H, d, J=1.6 Hz), 8.93 (1H, d, J=1.6 Hz)
2-1	2	4-thiazolyl	S	-81.8° (c=0.501, MeOH, 23 °C)		(CD_3OD) 8.95 (bs, 1H), 7.40 (bs, 1H), 4.6-5.0 (3H), 4.44 (d, J=8.6 Hz, 1H), 3.0-3.4 (4H), 1.39 (s, 9H)
3-1	3	5-thiazolyl	CH_2	-53.5° (c=1.000, MeOH, 23.5 °C)	216-218	($CDCl_3$) 8.88 (1H, s), 7.70 and 7.73 (total 1H, s), 4.57 (1H, dd, J=4.4, 9.9 Hz), 4.43 (1H, dd, J=4.2, 8.2 Hz), 3.72 (2H, m), 3.40 (1H, dd, J=4.4, 15.2 Hz), 3.12 (1H, dd, J=9.8, 15.2 Hz), 2.40-1.80 (4H, m), 1.38 (9H, s)

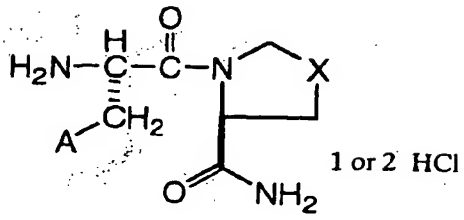
Example 1-process 2

Preparation of 3-(4-thiazolyl)-L-alanyl-L-prolineamide dihydrochloride (4)

[0048] To a solution of the compound (1, 5.53 g, 15 mmol) in ethyl acetate (30 ml) was added a solution of 4N-hydrochloride in ethyl acetate (75 ml, 300 mmol) under ice-cooling and the resulting mixture was stirred for 2.5 h at the same temperature. To the reaction mixture was added diethyl ether (400 ml) and the precipitation which appeared was filtered off. The precipitation was washed with diethyl ether and dried in vacuo with vacuum pump to give 6.67 g of the compound (4). This compound was used in the next reaction without purification.

The compounds (5) and (6) were synthesized in a manner similar to that described in the above method. The results were shown in Table 2.

Table 2



1 or 2 HCl

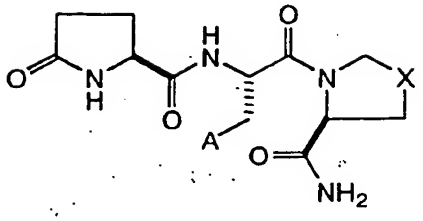
Example No.	Compound No.	A	X	$[\alpha]_D$	NMR
1-2	4	4-thiazolyl	CH_2	-29.0° (c=1.006, MeOH, 26 °C)	(D_2O) 9.53 (1H, d, J=2.1 Hz), 7.89 (1H, d, J=2.1 Hz), 4.66 (1H, t, J=5.7 Hz), 4.53 (1H, dd, J=5.4, 8.4 Hz), 3.50-3.7 (4H, m), 2.5-1.8 (4H, m)
2-2	5	4-thiazolyl	S		(D_2O) 9.12 and 9.10 (total 1H, s), 7.61 and 7.56 (total 1H, s), 4.9-4.7 (3H, m), 4.41 (1H, d, J=9.6 Hz), 3.4-3.6 (3H, m), 3.20 (1H, dd, J=5.8, 12.6 Hz)
3-2	6	5-thiazolyl	CH_2		(CD_3OD) 8.40 and 8.23 (total 1H, s), 4.72 (1H, t, J=5.4 Hz), 4.51 (1H, dd, J=5.4, 8.6 Hz), 4.20-3.40 (4H, m), 2.5-1.8 (4H, m)

Example 1- process 3

Preparation of L-pyroglutamyl-3-(4-thiazolyl)-L-alanyl-L-prolineamide dihydrochloride (I-1)

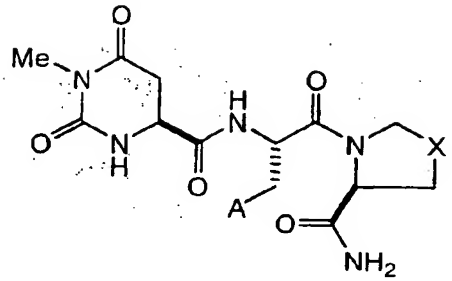
[0049] L-Pyroglutamic acid (1.76 g, 13.64 mmol) and N-hydroxysuccinimide (1.73 g, 15 mmol) were dissolved in N,N-dimethylformamide (50 ml). To this solution was added the solution of DCC (3.09 g, 15 mmol) in N,N- dimethylformamide (10 ml) under ice-cooling and the resulting mixture was stirred for 2h at the same temperature. 3-(4-thiazolyl)-L-alanyl-L-prolineamide dihydrochloride (4) (6.67 g, 15 mmol) and triethylamine (4.6 ml, 33 mmol) were added successively to the solution and the reaction mixture was stirred overnight. After the precipitation which appeared was filtered off, to the filtrate was added sodium hydrogencarbonate aq. to adjust pH 8. The reaction mixture was subjected to gel filtration column chromatography (MCI gel CHP-20P, 200 ml, aq. MeOH) to give the compound (I-1) (2.54 g, 49 %). The compounds (I-2) to (I-12) were synthesized in a manner similar to that described in the above method. The results were shown in Tables 3 to 6.

Table 3



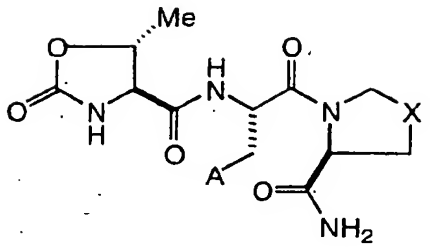
Example No.	Compound No.	A	X	[α]D	IR (cm-1)	NMR
1-3	I-1	4-thiazolyl	CH_2	-42.9° (c=1.003, MeOH, 24 °C)	(KBr) 3294, 1683, 1639, 1541, 1518, 1444, 1263	(CD_3OD) 8.95 (1H, d, J=2 Hz), 7.43 and 7.34 (total 1H, d, J=2 Hz), 4.95 (1H, t, J=7 Hz), 4.42 and 4.34 (total 1H, m), 4.17 (1H, m), 3.80 (1H, m), 3.1-3.6 (3H, m), 1.8-2.5 (8H, m).
2-3	I-2	4-thiazolyl	S	-87.6° (c=1.012, H_2O, 23 °C)	(KBr) 3301, 2936, 1685, 1518, 1419, 1330, 1262	(CD_3OD) 8.95 (1H, d, J=1.8 Hz), 7.43 and 7.37 (total 1H, d, J=1.8 Hz), 5.05 (1H, t, J=6.8 Hz), 4.99 (1H, d, J=8.6 Hz), 4.86 (1H, m), 4.45 (1H, d, J=8.6 Hz), 4.18 (1H, dd, J=5, 8.6 Hz), 3.1-3.5 (4H, m), 1.9-2.5 (4H, m)
3-3	I-3	5-thiazolyl	CH_2	-53.6° (c=1.002, MeOH, 23 °C)	(KBr) 3393, 3081, 1684, 1639, 1540, 1443, 1247	(CD_3OD) 8.86 (1H, s), 7.75 and 7.71 (total 1H, d, J=0.6 Hz), 4.90 (1H, m), 4.42 (1H, dd, J=4.5, 8.4 Hz), 4.18 (1H, dd, J=4.8, 8.7 Hz), 3.95-3.60 (2H, m), 3.50 (1H, dd, J=4.5, 15.3 Hz), 3.24 (1H, dd, J=9.3, 15.3 Hz), 2.60-1.80 (8H, m).

Table 4



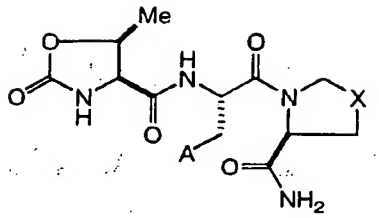
Example No.	Compound No.	A	X	[α]D	IR (cm⁻¹)	NMR
4-3	I-4	4-thiazolyl	CH_2	-10.4° (c=1.005, H_2O, 24 °C)	(KBr) 3397, 2954, 1719,1676, 1542(w), 1519(w),1448	(D_2O) 8.93 (1H, s), 7.35 and 7.29 (1H, s), 5.03 (1H, m), 4.39 (1H, m), 4.21 (1H, m), 3.76 (1H, m), 3.57 (1H, m), 2.7-3.4 (4H, m), 3.04 and 3.4 (4H, m), 3.04 and 3.01 (total 3H, s), 1.8-2.4 (4H, m).
5-3	I-5	4-thiazolyl	S	-37.3° (c=1.005, H_2O, 23 °C)	(KBr) 3313, 2931, 1720, 1675, 1517, 1468, 1435, 1305, 1125.	(CD_3OD) 8.93 (1H, d, J=1.8 Hz), 7.39 and 7.33 (total 1H, d, J=1.8 Hz), 5.02 (1H, t, J=6.8 Hz), 4.95 (1H, d, J=8.8 Hz), 4.86 (1H, m), 4.46 (1H, d, J=8.8 Hz), 4.09 (1H, dd, J=4.4, 7.2 Hz), 3.1-3.5 (4H, m), 3.06 (3H, s), 2.97 (1H, dd, J=7.2, 16.6 Hz), 2.78 (1H, dd, J=4.2, 16.6 Hz)
6-3	I-6	5-thiazolyl	CH_2	-12° (c=1.011, MeOH, 23 °C)	(KBr) 3318, 1720, 1675, 1523, 1448, 1356, 1304, 1270.	(CD_3OD) 8.87 (1H, s), 7.67 and 7.73 (total 1H, s), 4.90 (1H, m), 4.42 (1H, dd, J=4.4, 8.2 Hz), 4.09 (1H, dd, J=3.6, 7 Hz), 3.70 (2H, m), 3.49 (1H, dd, J=4.2, 15.4 Hz), 3.21 (1H, dd, J=9.2, 15.4 Hz), 3.08 and 3.05 (total 3H, s), 2.92 (1H, dd, J=7, 12.6 Hz), 2.78 (1H, dd, J=3.6, 12.6 Hz), 2.4-1.8 (4H, m).

Table 5



Example No.	Compound No.	A	X	[α]D	IR (cm-1)	NMR
7-3	I-7	4-thiazolyl	CH_2	-30.3° (c=1.003, H_2O, 25°C)	(KBr) 3398, 1752, 1677, 1641, 1517, 1445, 1229.	(CD_3OD) 8.95 (1H, d, J=2 Hz), 7.43 and 7.33 (1H, d, J=2 Hz), 4.97 (1H, t, J=7 Hz), 4.3-4.6 (2H, m), 3.93 (1H, d, J=5.4 Hz), 3.78 (1H, m), 3.1-3.6 (3H, m), 1.7-2.3 (4H, m), 1.45 (3H, d, J=6.6 Hz).
8-3	I-8	4-thiazolyl	S	-58.8° (c=1.010, H_2O, 23°C)	(KBr) 3397, 2980, 2932, 1752, 1677, 1649, 1519, 1413, 1227	(CD_3OD) 8.95 (1H, d, J=1.8 Hz), 7.43 and 7.36 (1H, d, J=1.8 Hz), 5.07 (1H, t, J=6.6 Hz), 4.98 (1H, d, J=8.6 Hz), 4.86 (1H, m), 4.4-4.6 (1H, m), 4.45 (1H, d, J=8.6 Hz), 3.95 (1H, d, J=5 Hz), 3.1-3.5 (4H, m), 1.46 (3H, d, J=6.2 Hz).
9-3	I-9	5-thiazolyl	CH_2	-25.8° (c=1.009, H_2O, 23°C)	(KBr) 3397, 1753, 1677, 1639, 1527, 1446, 1403, 1301, 1230	(CD_3OD) 8.89 (1H, s), 7.76 and 7.71 (total 1H, s), 4.90 (2H, m), 4.43 (1H, dd, J=5.4, 6.3 Hz), 3.93 (1H, d, J=5.4 Hz), 4.1-3.6 (2H, m), 3.50 (1H, dd, J=4.2, 15 Hz), 3.25 (1H, dd, J=9.3, 15 Hz), 2.4-1.8 (4H, m), 1.44 (3H, d, J=6.3 Hz).

Table 6



Example No.	Compound No.	A	X	$[\alpha]_D$	IR (cm^{-1})	NMR
10-3	I-10	4-thiazolyl	CH_2	-52.1° (c=1.006, H_2O, 26 °C)	(KBr) 3392, 1751, 1676, 1638, 1542, 1519, 1446, 1407, 1235, 1097	(CD_3OD) 8.95 (1H, d, J=1.8 Hz), 7.43 and 7.35 (total 1H, d, J=1.8 Hz), 5.02 (1H, t, J=7.1 Hz, 1H), 4.90 (1H, m), 4.38 (1H, m), 4.33 (1H, d, J=8.6 Hz), 3.88 (1H, m), 3.1-3.6 (3H, m), 1.9-2.3 (4H, m), 1.26 and 1.20 (total 3H, d, J=6.6 Hz).
11-3	I-11	4-thiazolyl	S	-80.3° (c=1.010, H_2O, 23 °C)	(KBr) 3308, 2985, 2936, 1752, 1678, 1651, 1518, 1414, 1333, 1231, 1096	(CD_3OD) 8.99 and 8.95 (total 1H, d, J=2 Hz), 7.43 and 7.39 (total 1H, d, J=2 Hz,), 5.11 (1H, t, J=6.5 Hz), 5.10 (1H, d, J=8.6 Hz), 4.7-5.0 (2H, m), 4.48 (1H, d, J=8.6 Hz), 4.34 (1H, d, J=8.8 Hz), 3.1-3.5 (4H, m), 1.22 (3H, d, J=6.6 Hz)
12-3	I-12	5-thiazolyl	CH_2	-46.2° (c=1.002, MeOH, 23 °C)	(KBr) 3406, 1752, 1677, 1638, 1542, 1447, 1404, 1343, 1300, 1237	(CD_3OD) 8.89 and 8.80 (total 1H, s), 7.73 and 7.77 (total 1H, s), 4.90 (1H, m), 4.90 (1H, m), 4.41 (1H, dd, J=5.2 and 9 Hz), 4.35 (1H, d, J=8.7 Hz), 3.90 (1H, m), 3.71 (1H, m), 3.50 (1H, dd, J=4.2, 15.3 Hz), 3.25 (1H, dd, J=9.6, 15.3 Hz), 2.4-1.8 (4H, m), 1.26 and 1.18 (total 3H, d, J=6.3 Hz).

Example 13

Preparation of L-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-prolineamide (I-13)

[0050] The compound (I-13) was obtained in a manner similar to that described in the method of Example 1-3.

Example 14

Preparation of trans-L-N-benzyl-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-prolineamide (I-14).

[0051] (1) trans-L-5-Methyl-2-oxo-oxazolidine-4-carboxylic acid benzyl ester (706 mg, 3 mmol) which was synthesized in accordance with the method described in Tetrahedron Lett., 36, 6569 (1995) was dissolved in N, N-dimethylformamide (8 ml). After benzyl bromide (0.39 ml, 3.28 mmol) was added to the solution, 60% sodium hydride (120 mg, 3 mmol) was added to the mixture over 5 min. with stirring. The mixture was stirred for 3h at room temperature. The reaction mixture was partitioned between ice-water and ethyl acetate. The organic layer was washed with water, dried over magnesium sulphate, and concentrated in vacuo. The residue was subjected to Lobar® column B (Merck inc.) and the fractions eluting with toluene : acetone = 30:1 were collected to yield trans-L-N-benzyl-5-methyl-2-oxo-oxazolidine-4-carboxylic acid benzyl ester (859 mg, 88.%) as colorless oil.

NMR ($CDCl_3$) : 7.1-7.5 (10H, m), 5.17 (2H, s), 4.92 (1H, d, J=14.6 Hz), 4.56 (1H, m), 4.14 (1H, d, J=14.6 Hz), 3.63 (1H, d, J=5.2 Hz), 1.39 (3H, d, J=6.4 Hz).

[0052] The compound (850 mg, 2.61 mmol) obtained in the above process was dissolved in mixed solvents of tetrahydrofuran (18 ml) and 1,2-dimethoxyethane (2.7 ml). To the mixture was added the solution of lithium hydroxide monohydrate (548 mg, 13.1 mmol) in water (10 ml) and the resulting mixture was stirred for 30 min. at room temperature. The reaction mixture was poured into ice-water and extracted with diethyl ether three times. To the alkali layer was added 5N hydrochloric acid (3 ml) for adjusting pH 1 and the mixture was extracted with ethyl acetate twice. The organic layer was washed with water, dried over magnesium sulphate, and concentrated in vacuo. The residue (574 mg, 93.5 %) was recrystallized from acetone - hexane to give trans-L-N-benzyl-5-methyl-2-oxo-oxazolidine-4-carboxylic acid (493 mg, 80.3 %).

mp : 127°C
$[\alpha]_D$ = -7.8° (c=1.003, $CHCl_3$, 24 °C)
IR (KBr) cm^{-1} : 2716, 2601, 1740, 1692, 1497, 1442, 1421, 1369, 1248, 1201, 1186, 1078.
IR ($CHCl_3$) cm^{-1} : 1758, 1496, 1455, 1415, 1227, 1223, 1212, 1205.
NMR (DMSO-d6) : 7.2-7.5 (5H, m), 4.69 (1H, d, J=15.4 Hz), 4.62 (1H, m), 4.15 (1H, d, J=15.4 Hz), 3.71 (1H, d, J=4.4 Hz), 1.32 (3H, d, J=6.2 Hz).
Elemental analysis ($C_{12}H_{13}NO_4$)

Calcd. :	C,61.27;	H,5.57;	N,5.96.
Found :	C,61.30;	H,5.61;	N,5.91.

[0053] Compound (I-14) was obtained in a manner similar to that described in the Example 1-3.

Example 15

Preparation of trans-L-N,5-dimethyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-prolineamide (I-15)

[0054] To a solution of trans-L-5-methyl-2-oxo-oxazolidine-4-carboxylic acid benzyl ester (488 mg, 2.075 mmol) in N, N-dimethylformamide (6 ml) was added iodomethane (0.17 ml, 2.73 mmol) under ice-cooling in nitrogen atmosphere with stirring. Subsequently, 60 % sodium hydride (83 mg, 2.075 mmol) was added to the mixture over 10 min. The reaction mixture was stirred for 3h at the same temperature. The reaction mixture was partitioned between ice-water and ethyl acetate. The organic layer was washed with water, dried over magnesium sulphate, and concentrated in vacuo. The residue (503 mg) was subjected to Lobar® column B (Merck inc.) and the fractions eluting with toluene : acetone

= 30:1 were collected to yield trans-L-N,5-dimithyl-2-oxo-oxazolidine-4-carboxylic acid benzyl ester (444 mg, 85.8 %) as colorless oil.

NMR($CDCl_3$): 7.37 (5H, m), 5.27 (1H, d, J=12.2 Hz), 5.20 (1H, d, J=12.2 Hz), 4.51 (1H, m), 3.86 (1H, d, J=5.4 Hz), 2.92(3H, s), 1.50 (3H. d, J=6.2 Hz)..

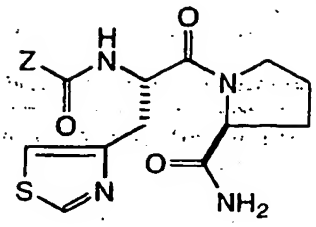
[0055] A solution of the compound (551 mg, 2.21 mmol) which was obtained the above process in mixed solvents of methanol (10 ml) - water (1 ml) was hydrogenated using 5 % Pd/C (150 mg) for 1h at room temperature. The catalyst was filtered off and the filtrate was concentrated in vacuo to obtain trans-L-N,5-dimethyl-2-oxo-oxazolidine-4-carboxylic acid (345 mg, 98%).

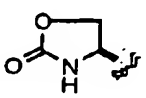
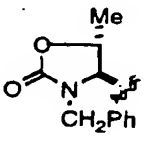
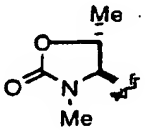
mp: 125 - 127 °C
$[\alpha]_D$ = -11.1° (c=1.005, MeOH, 24 °C)
IR(KBr)cm^{-1}: 3433, 2585, 1743, 1697, 1483, 1443, 1408, 1227, 1034.
NMR(DMSO-d6): 4.51 (1H, m), 3.99 (1H, d, J=5.4 Hz), 2.79 (3H, s), 1.38 (3H, d, J=6.2 Hz).
Elemental analysis ($C_6H_9NO_4$)

Calcd. :	C,45.28;	H,5.70;	N,8.80.
Found :	C,45.40;	H,5.63;	N,8.74.

[0056] The compound (I-15) was obtained in a manner similar to that described in the method of Example 1-3. The results were shown in Table 7.

Table 7



Example No.	Compound No.	Z	[α]D	IR (cm-1)	NMR
13	I-13		-53.0° (c=1.009, H_2O, 25°C)	(KBr)3294,1752,1676,1637,1542,1519,1446,1407,1237	(CD_3OD) 8.95 (1H, d, J=2 Hz), 7.43 and 7.33 (total 1H, d, J=2 Hz), 4.96 (1H, t, J=7.1 Hz), 4.2-4.6 (4H, m), 3.80 (1H, m), 3.1-3.6 (3H, m), 1.9-2.3 (4H, m)
14	I-14		-43.7° (c=1.008, H_2O, 24.5 °C)	(KBr)3412,1752,1679,1644,1543,1516,1442,1415,1227,1206,1092,1066.	(CD_3OD) 8.99 (1H, d, J=2 Hz), 7.41 (1H, d, J=2.1 Hz),7.1-7.5 (5H, m), 4.95 (1H, m), 4.73 (1H, d, J=15.2 Hz), 4.42 (2H, m), 3.87 (2H, d, J=15.2 Hz), 3.78 (1H, m), 3.68 (1H, d, J=5.1 Hz), 3.0-3.6 (3H, m), 1.8-2.3 (4H, m), 1.35 (3H, d, J=6.4 Hz).
15	I-15		-31.9° (c=1.000, H_2O, 23°C)	(KBr)3412,1751,1678,1519,1544,1519,1437,1401,1237.	(CD_3OD) 8.96 (1H, d, J=2 Hz), 7.44 and 7.35 (total 1H, d, J=2 Hz), 5.04 (1H, dd, J=6.2, 7.8 Hz), 4.40 (2H, m), 3.88 (1H, d, J=5.4 Hz), 3.80 (1H, m), 3.1-3.6 (3H, m), 2.67(3H, s), 1.8-2.3 (4H, m), 1.43 (3H, d, J=6.4 Hz)

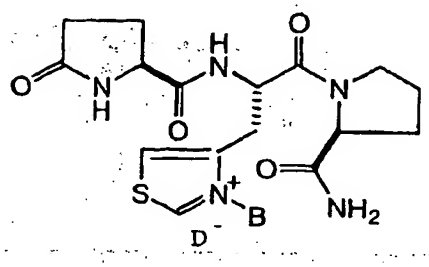
Example 16

Preparation of 4-[2-L-pyroglutamyl-2-{(S)-2-carbamoylpyrrolidine-1-ylcarbonyl}ethyl]-3-methylthiazolium iodide (I-16)

[0057] To a solution of the compound (I-1) (5 g, 13.18 mmol) in acetonitrile (500 ml) was added iodomethane (67 ml, 1.07 mol) and the resulting mixture was heated at reflux on oil bath (80°C) for 20h. After the reaction mixture was cooled at 0°C, the supernatant liquid was removed by decanting. The precipitate was washed with cold acetonitrile and was added diethyl ether. The crystal powder was collected by filtration to give 6.64 g of compound (I-16) as yellow powder.

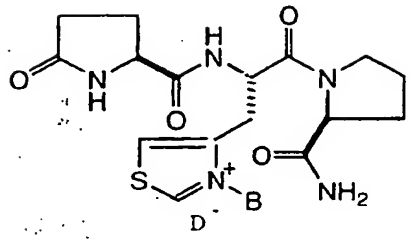
Using a procedure analogous to that described above, the compounds (I-17) to (I-27) were synthesized. The results were shown in Table 8 to Table 10.

Table 8



Example No.	Compound No.	B	D	NMR(CD_3OD)
16-3	I-16	Me	I	8.03 and 7.96 (total 1H, s), 5.13 (1H, t, J=7 Hz), 4.58 and 4.42 (total 1H, m), 4.31 and 4.26 (total 3H, s), 4.20 (1H, m), 3.66 (2H, m), 3.50 (1H, dd, J=6.6 and 15.6 Hz), 3.25 (1H, dd, J=7.4, 15.6 Hz), 1.8-2.5 (8H, m)
17-3	I-17	Et	I	10.08 (1H, s), 8.04 and 7.97 (total 1H, s), 5.12 (1H, t, J=7.6 Hz), 4.62 (2H, q, J=7.2 Hz), 4.42 (1H, m), 4.19 (1H, m), 3.2-3.7 (4H, m), 2.32 (4H, m), 1.98 (4H, m), 1.66 (3H, t, J=7.2 Hz).
18-3	I-18	n-Pr	I	10.08 (1H, d, J=2.6 Hz), 8.06 and 8.00 (total 1H, d, J=2.6 Hz), 5.12 and 4.98 (total 1H, t, J=7.0 Hz), 4.56 (2H, t, J=7.8 Hz), 4.43 (1H, m), 4.20 (1H, m), 3.2-3.9 (4H, m), 2.34 (4H, m), 2.02 (6H, m), 1.18 and 1.07 (total 3H, t, J=7.4 Hz).
19	I-19	n-Bu	I	10.07 (1H, d, J=2.6 Hz), 8.06 and 7.99 (total 1H, d, J=2.6 Hz), 5.12 and 4.99 (total 1H, t, J=7.0 Hz), 4.59 (2H, t, J=7.8 Hz), 4.43 (1H, m), 4.20(1H, m), 3.2-3.9 (4H, m), 2.34 (4H, m), 2.02 (6H, m), 1.49 (2H, m), 1.04 (3H, t, J=7.0 Hz).

Table 9



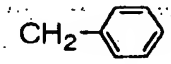
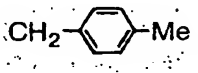
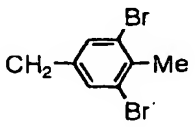
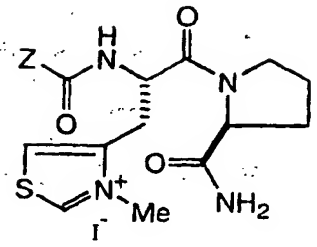
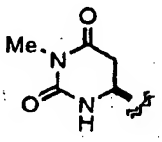
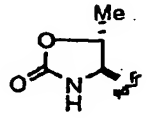
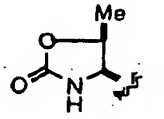
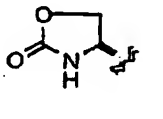
Example No.	Compound No.	A	X	$[\alpha]_D$	NMR(CD_3OD)
20	I-20	allyl	Br		8.65 (1H, d, J=9.3 Hz), 8.08 (1H, d, J=2.7 Hz), 6.17 (1H, m), 5.47 (2H, m), 5.25 (2H, m), 5.11 (1H, m), 4.41 (1H, dd, J=4.2, 8.8 Hz), 4.19 (1H, dd, J=4.8, 8.8 Hz), 3.66 (2H, m), 3.50 (1H, dd, J=7.2, 15 Hz), 3.25 (1H, m), 1.8-2.5 (8H, m).
21	I-21		Br	-70.5° (c=1.005, H_2O, 24°C)	9.90 and 9.86 (total 1H, d, J=2.4 Hz), 8.12 and 8.03 (total 1H, d, J=2.4 Hz), 7.47 (5H, m), 5.89 (1H, d, J=15.2 Hz), 5.80 (1H, d, J=15.2 Hz), 5.04 (1H, t, J=7 Hz), 4.40 (1H, m), 4.20 (1H, m), 3.1-3.7 (4H, m), 2.35 (4H, m), 1.97 (4H, m).
22	I-22		Br	-65.4° (c=1.001, H_2O, 24°C)	9.12 and 8.02 (total 1H, d, J=2.4 Hz), 7.32 (4H, m), 5.82 (1H, d, J=15 Hz), 5.73 (1H, d, J=15 Hz), 5.02 (1H, t, J=7 Hz), 4.40 (1H, m), 4.20 (1H, m), 3.1-3.7 (4H, m), 2.37 (3H, s), 2.34 (4H, m), 1.97 (4H, m).
23	I-23		Br		9.71 (1H, d, J=2.4 Hz), 7.02 (1H, d, J=2.7 Hz), 5.62 (2H, d, J=4.2), 5.04 (1H, m), 4.42 (1H, m), 4.19 (1H, dd, J=4.2, 8.5 Hz.) ,3.66 (2H, m), 3.50 (1H, m), 3.25 (1H, m), 2.22 (6H, s). 1.8-2.5 (8H, m).

Table 10



Example No.	Compound No.	Z	$[\alpha]_D$	NMR(CD_3OD)
24	I-24		-26.9° (c=1.001, H_2O, 22.5°C)	7.91 and 7.88 (total 1H, s), 5.12 (1H, dd, J=5.1 and 9.9 Hz), 4.44 and 4.55 (total 1H, m), 4.13 and 4.26 (total 1H, m), 4.23 (3H, s), 3.63 (2H, m), 3.48 (1H, dd, J=4.5 and 15.6 Hz), 3.31 (1H, dd, J=9.6 and 1 5.6 Hz), 3.11 (1H, dd, J=6.9, 16.8 Hz), 3.05 (3H, s,), 2.76 (1H, dd), 1.8-2.4 (4H, m).
25	I-25		-42.9° (c=1.013, H_2O, 24.5°C)	8.04 and 7.94 (total 1H, s), 5.16 (1H, dd, J=6.4, 7.8 Hz), 4.4-4.6 (2H, m), 4.30 and 4.26 (total 3H, s), 3.98 and 3.90 (total 1H, d, J=5.4 Hz), 3.66 (2H, m), 3.52 (1H, dd, J=6.6, 16.0 Hz), 3.27 (1H, dd, J=8.2, 16 Hz), 1.8-2.4 (4H, m), 1.46 (3H, d, J=6.2 Hz).
26	I-26		-50.0° (c=1.006, H_2O, 24.5°C)	8.09 and 8.02 (total 1H, s), 5.19 (1H, t, J=7 Hz), 4.8-5.0 (1H, m), 4.3-4.5 (2H, m), 4.30 and 4.24 (total 3H, s), 3.82 (1H, m), 3.64 (1H, m), 3.53 (1H, dd, J=7, 15.6 Hz), 3.26 (1H, m), 1.8-2.4 (4H, m), 1.27 (3H, d, J=6.4 Hz).
27	I-27		-59.2° (c=1.006, H_2O, 24.5°C)	8.03 and 7.95 (total 1H, s), 5.15 (1H, dd, J=6.4, 7.8 Hz), 4.58 (1H, dd, J=8.4, 9 Hz), 4.42 (1H, dd, J=4.6, 9 Hz), 4.2-4.5 (2 H, m), 4.30 and 4.26 (total 3H, s), 3.67 (2H, m), 3.52 (1H, dd, J=7.4, 15.8 Hz), 3.27 (1H, dd, J=8, 15.8 Hz), 1.8-2.4 (4H, m).

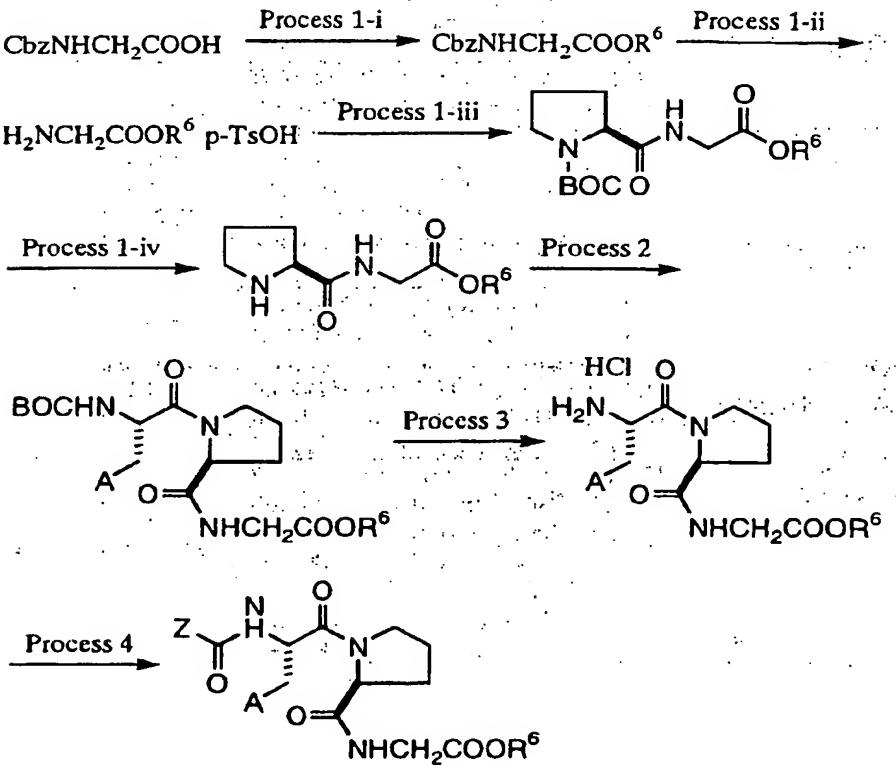
Example 28

Preparation of 5-[2-L-pyroglutamylamino-2-[(S)-2-carbamoylpyrrolidine-1-ylcarbonyl] ethyl]-3-methylthiazolium iodide (I-28)

[0058] The compound (I-28) was obtained 56.4 % yield in a manner similar to that described in the method of Example 16 using the compound (I-3) as a starting material.

$[\alpha]_D$ = -40.6° (c=1.001; MeOH, 21°C)
IR(KBr)cm^{-1}: 3412, 1677, 1639, 1533, 1439, 1262.
NMR(CD_3OD): 8.20 and 8.21 (total 1H, s), 5.02 (1H, dd, J=6,7 Hz), 4.41 (1H, dd, J=4,8. 4 Hz), 4.25 (1H, dd, J=3, 5.8 Hz), 4.22 (3H, s), 3.68 (2H, m), 3.53 (1H, dd, J=7, 15 Hz), 3.34 (1H, dd, J=6, 15 Hz), 1.8-2.4 (4H, m), 2.02 (4H, m).
Elemental analysis ($C_{17}H_{24}N_5O_4IS\ 3H_2O$)

Calcd. :	C,35.48;	H,5.25,	N,12.17;	I,22.05;	S,5.57.
Found :	C,35.36;	H,5.15;	N,12.43;	I,21.97;	S,5.75.
Found :	C,35.36;	H,5.15;	N,12.43;	I,21.97;	S,5.75.



Example 29- process 1

Preparation of tetradecyl L-prolyl-glycinate (10)

[0059]

(i) To a solution of N-benzyloxycarbonyl glycine (3 g, 14.3 mmol), tetradecylalcohol (3.07 g, 14.3 mmol) and N, N-dimethylaminopyridine (87 mg, 10.3 mmol) in ethyl acetate (100 ml) was added DCC (2.98 g, 2.34 mmol) and the resulting mixture was stirred for 2h at room temperature. After the precipitation which appeared was filtered off, the filtrate was concentrated in vacuo. The residue was washed with ethanol to give N-benzyloxycarbonylglycine tetradecyl ester (7) (3.46 g, 59.5 %) as crystal.

mp : 57 - 58°C
NMR($CDCl_3$): 7.36 (5H, s), 5.22 (1H, m), 5.13 (2H, s), 4.14 (2H, t, J=6.6 Hz), 3.84 (2H, d. J=5.4 Hz), 1.60 (2H, m), 1.26 (22H ,br.s). 0.88 (3H, t, J=6.6 Hz). Elemental analysis ($C_{24}H_{39}NO_4$)

Calcd. :	C,71.07;	H,9.69;	N,3.45.
Found :	C,70.94;	H,9.60;	N,3.74.

(ii) A solution of the compound (7) and p-toluenesulfonic acid hydrate (1.4 g, 7.39 mmol) in mixed solvents of water (2 ml) - methanol (70 ml) was hydrogenated using 5 % pd/C (500 mg) for 3h at room temperature. After the catalyst was filtered off, the filtrate was concentrated in vacuo. The residue was recrystallized from ethyl acetate to give tetradecanylglycinate p-toluensulfonate (8) (2.76 g, 84 %).

mp : 85.5 - 86.5°C
NMR(CD_3OD): 7.70 (2H, d, J=8.2 Hz), 7.23 (2H, d, J=8.2 Hz), 4.23 (2H, d, J=6.6 Hz), 3.82 (2H, s), 2.37 (3H, s), 1.65 (2H, m), 1.29 (22H, m), 0.90 (3H, t, J=6.6 Hz).
Elemental analysis ($C_{23}H_{41}NSO_5$)

Calcd. :	C,62.12;	H,9.29;	N,3.15;	S,7.21.
Found :	C,61.90;	H,9.15;	N,3.18;	S,7.72.

(iii) To a solution of the compound (8) (2.06 g, 4.64 mmol), N-(tert-butyloxycarbonyl)-L-proline (1 g, 4.64 mmol), N-hydroxybenzotriazole (18 mg, 0.139 mmol), and triethylamine (0.71 ml) in N, N-dimethylformamide (30 ml) was added DCC (1 g, 4.87 mmol) and the resulting mixture was stirred for 18h at room temperature. After the precipitation which appeared was filtered off, the filtrate was concentrated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was washed with water, dried over magnesium sulphate, and concentrated in vacuo. The residue was subjected to silica gel column chromatography (toluene : ethyl acetate = 3:1) to give tetradecyl N-(tert-butyloxycarbonyl)-L-prolyl-glycinate (9) (1.94 g, 89.4 %).

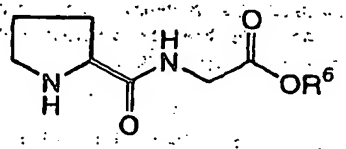
$[\alpha]_D$ = -54.4° (c=1.008, $CHCl_3$, 23°C)
NMR($CDCl_3$) : 4.31 (1H, m), 413 (2H t, J=6.6 Hz), 4.05 (2H, dd, J=5.8, 7.7 Hz), 3.45 (2H, m), 1.90 (2H, m), 1.47 (9H, s), 1.26 (22H, br.s). 0.88 (3H, t. J=7 Hz).
Elemental analysis ($C_{26}H_{48}N_2O_5$)

Calcd. :	C,66.63;	H,10.32;	N,5.98.
Found :	C,66.62;	H,10.24;	N,6.05.

(iv) A suspension of the compound (9) (1.47 g, 3.02 mmol) in trifluoroacetic acid (14 ml) was stirred for 2h under

ice-cooling. The reaction mixture was diluted with toluene and the resulting mixture was concentrated in vacuo. The residue was partitioned between ethyl acetate and sodium hydrogencarbonate aq. The organic layer was washed with water and concentrated in vacuo to give 1.08 g of tetradecyl L-prolyl-glycinate (10) as powder.
The compounds (11) and (12) were synthesized in a manner similar to that described in the above method. The results were shown in Table 11.

Table 11



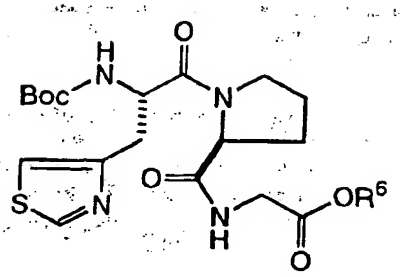
Example No.	Compound No.	R^6	$[\alpha]_D$	NMR
29-1	10	$(CH_2)_{13}CH_3$	-45.7° (c=1.004, MeOH, 23°C)	($CDCl_3$) 8.10 (1H, m), 4.13 (2H, t, J=6.6 Hz), 4.03 (2H, d, J=5.6 Hz), 3.79 (1H, dd, J=5.4, 9 Hz), 3.00 (2H, m), 1.8-2.2 (2H, m), 1.70 (4H, m), 1.26 (22H, m), 0.88 (3H, t, J=6.8 Hz).
30-1	11	$CH(CH_3)_2$		(CD_3OD) 7.36 (5H, s), 5.18 (1H, d, J=7 Hz), 4.31 (1H, m), 4.08 (2H, m), 3.35 (2H, m), 2.44 (1H, m), 2.05 (3H, m)
31-1	12	CH_2Ph		(CD_3OD) 5.03 (1H, m), 4.33 (1H, m), 4.00 (2H, m), 3.35 (2H, m), 2.48 (1H, m), 2.06 (3H, m), 1.24 (6H, d, J=6 Hz)

Example 29- process 2

Preparation of tetradecyl N-(tert-butyloxycarbonyl)-3-(4-thiazolyl)-L-alanyl-L-prolyl-glycinate (13)

[0060] To a solution of N-(tert-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine (1, 480 mg, 1.76 mmol) which was synthesized in accordance with the method described in the literature (Synthtic Commun., 20, 3507, (1990)), the compound (10) (650 mg, 1.76 mmol), and N-hydroxybenzotriazole (70 mg, 0.528 mmol) in N, N-dimethylformamide (20 ml) was added DCC (380 mg, 1.848 mmol) and the resulting mixture was stirred overnight at room temperature. After the precipitation which appeared was filtered off, the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate and the precipitation which appeared was filtered off again. The filtrate was concentrated in vacuo. The residue was subjected to silica gel column chromatography (ethyl acetate : toluene = 9:1) to give 1.02 g of the compound (13).
The compounds (14) and (15) were synthesized in a manner similar to that described in the above method. The results were shown in Table 12.

Table 12



Example No.	Compound No.	R^6	$[\alpha]_D$	NMR ($CDCl_3$)
29-2	13	$(CH_2)_{13}CH_3$	-44.9° (c=1.012, $CHCl_3$, 23°C)	8.78 (1H, d, J=1.8 Hz), 7.22 (1H, d, J=2 Hz), 5.54 (1H, d, J=8.2 Hz), 4.67 (2H, m), 4.41 (1H, dd, J=7.4, 17.6 Hz), 4.14 (2H, t, J=7 Hz), 3.74 (1H, dd, J=5.5, 17.6 Hz), 3.50 (1H, m), 3.30 (2H, m), 2.97 (1H, m), 1.45 (9H, s), 2.30 (1H, m), 1.95 (3H, m), 1.27 (22H, m), 0.89 (3H, t, J=6.6 Hz).
30-2	14	$CH(CH_3)_2$	-43.2° (c=1.012, $CHCl_3$, 23°C)	8.80 (1H, s), 8.60 (1H, m), 7.22 (1H, s), 5.78 (1H, m), 5.07 (1H, m, COOCH), 4.64 (2H, m), 1.45 (9H, s), 1.29 (3H, d, J=6 Hz), 1.27 (3H, d, J=6 Hz)
31-2	15	CH_2Ph	-49.4° (c=1.01, $CHCl_3$, 23°C)	8.58 (1H, d, J=2 Hz), 7.36 (5H, s), 7.18 (1H, d, J=1.8 Hz), 5.50 (1H, d, J=6.8 Hz), 4.64 (2H, m), 4.47 (1H, dd, J=6.8, 17.5 Hz), 3.77 (1H, dd, J=5, 17.5 Hz), 3.50 (1H, m), 3.30 (2H, m), 2.95 (1H, m), 2.2-1.7 (4H, m), 1.44 (9H, s)

Example 29-process 3

Preparation of tetradecyl 3-(4-thiazolyl)-L-alanyl-L-prolyl-glycinate hydrochloride (16)

[0061] To a solution of the compound (13) (1.2 g, 1.92 mmol) in ethyl acetate (20 ml) was added the solution of 4N-hydrogen chloride in ethyl acetate (20 ml) under ice-cooling and the resulting mixture was stirred for 2h at the same temperature. The reaction mixture was concentrated in vacuo to give the compound (16) (1.27 g, quantitative). This compound used in the next reaction without purification.

Example 30- process 3

Preparation of isopropyl 3-(4-thiazolyl)-L-alanyl-L-prolyl-glycinate hydrochloride (17)

[0062] In a manner similar to that described in the method of Example 29-3, the compound (17) (590 mg, quantitative)

was obtained by de-tert-butoxycarbonylation of compound (14) (580 mg, 1.24 mmol). This compound was used in the next reaction without purification.

Example 31- process 3

Preparation of benzyl 3-(4-thiazolyl)-L-alanyl-L-prolyl-glycinate hydrochloride (18)

[0053] In a manner similar to that described in the method of Example 29-3, the compound (18) (700 mg, quantitative) was obtained by de-tert-butoxycarbonylation of the compound (15) (750 mg, 1.45 mmol). This compound was used in the next reaction without purification.

Example 29- process 4

Preparation of tetradecyl cis-L-5-methyl-2-oxo-oxazolidine-4-ylcarbonyl-3-(4-thiazolyl)-L-alanyl-L-prolyl-glycinate (I-29)

[0054] Cis-5-methyl-2-oxazolidine-4-yl carboxylic acid (139 mg 0.96 mmol), which was synthesized in accordance with the method described in Chem. Lett., 1982, 1171 and N-hydroxysuccinimide (110 mg, 0.96 mmol) were dissolved in N, N-dimethylformamide (2 ml). To this solution was added DCC (200 mg, 0.97 mmol) and the resulting mixture was stirred for 2h at room temperature. To the reaction mixture was added the free base of the compound (16) prepared by filtering off the salt which was precipitated by adding triethylamine (0.53 ml, 3.8 mmol) to the solution of the compound (16) (635 mg. 0.96 mmol) in N, N-dimethylformamide (15 ml) under ice-cooling. The reaction mixture was stirred for 72h at room temperature. After the precipitation which appeared was filtered off and the filtrate was concentrated in vacuo. Mixed solvents of methanol : water =3:1 was added to the residue and the precipitation which appeared was filtered off. The filtrate was subjected to gel filtration column chromatography (MCI Gel CHP 20P 200 ml, methanol - water) and successively to silica gel column chromatography (chloroform : methanol = 7:1) to give 381 mg of the compound (I-29).

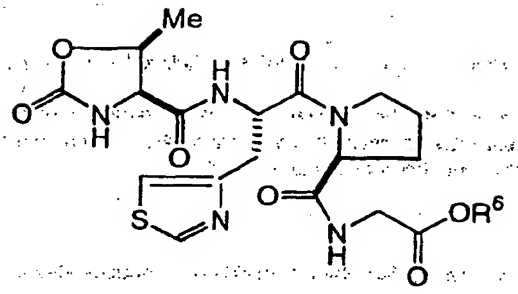
[0055] The compounds (I-30) and (I-31) was synthesized in a manner similar to that described in the above method. The results were shown in Table 13.

Example 32

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-ylcarbonyl-3-(4-thiazolyl)-L-alanyl-L-prolyl-glycine (I-32)

[0056] To a solution of the compound (I-31) (500 mg, 0.919 mmol) in mixed solvents of methanol (20 ml) - water (20 ml) was added lithium hydroxide (193 mg, 4.56 mmol) and the resulting mixture was stirred for 30 min at room temperature. After the reaction mixture was neutralized by adding the diluted hydrochloric acid, the mixture was concentrated in vacuo. The residue was subjected to gel filtration column chromatography (MCI Gel CHP 20P, 200 ml, methanol - water) and further lyophilized to give 218 mg of the compound (I-32). The result was shown in Table 13.

Table 13



Example No.	Compound No.	R^6	$[\alpha]_D$	NMR (CD_3OD)
29-4	I-29	$(CH_2)_{13}CH_3$	-54.7° (c=0.505, MeOH, 23°C)	8.95 (1H, d, J=1.2 Hz), 8.58 (2H, m), 7.45 (1H, s), 4.90 (2H, m), 4.49 (1H, m), 4.34 (1H, d, J=8.6 Hz), 4.14 (2H, t, J=6.6 Hz), 3.96 (2H, d), 3.87 (1H, m), 3.30 (3H, m), 1.28 (3H, d, J=6.6 Hz), 0.89 (3H, t, J=6.6 Hz).
30-4	I-30	$CH(CH_3)_2$	-68.7° (c=0.504, MeOH, 25°C)	8.78 (1H, d, J=1.8 Hz), 7.22 (1H, d, J=2 Hz), 5.54 (1H, d, J=8.2 Hz), 4.67 (2H, m), 4.41 (1H, dd, J=7.4, 17.6 Hz), 4.14 (2H, t, J=7 Hz), 3.74 (1H, dd, J=5.5, 17.6 Hz), 3.50 (1H, m), 3.30 (2H, m), 2.97 (1H, m), 1.45 (9H, s), 2.30 (1H, m), 1.95 (3H, m), 1.27 (22H, m), 0.89 (3H, t, J=6.6 Hz).
31-4	I-31	CH_2Ph	-61.8° (c=0.508, MeOH, 23°C)	8.88 (1H, s), 7.42 (1H, s), 7.35 (5H, m), 5.18 (2H, s), 4.95 (2H, m), 4.47 (1H, dd, J=4.2, 8.6 Hz), 4.33 (1H, d, J=8.7 Hz), 4.07 (1H, d, J=17.7 Hz), 3.99 (1H, d, J=17.7 Hz), 3.80 (1H, m), 3.60 (1H, dd, J=6.9, 14 Hz), 3.35 (1H, m), 3.22 (1H, m), 2.2-1.9 (4H, m), 1.21 (3H, d, J=6.6 Hz)
32	I-32	H	-69.2° (c=0.507, H_2O, 22.5°C)	8.99 (1H, d, J=1.4 Hz), 7.44 (1H, d, J=1.4 Hz), 4.95 (2H, m), 4.47 (1H, t, J=5.4 Hz), 4.34 (1H, d, J=8.8 Hz), 3.87 (1H, d, J=17.2 Hz), 3.67 (1H, d, J=17.2 Hz), 3.80-3.20 (4H, m), 2.2-1.8 (4H, m), 1.21 (3H, d, J=6.2 Hz)

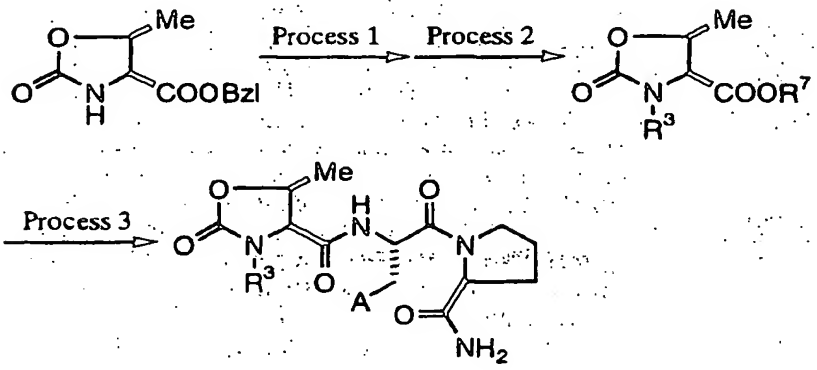
Example 33

Preparation of tetradecyl L-pyroglutamyl-3-(4-thiazolyl)-L-alanyl-L-prolyl-glycinate (I-33)

[0057] In a manner similar to that described in the method of Example 29-4, N-hydroxysuccinimide ester of L-pyroglutamic acid which are prepared by the reaction of L-pyroglutamic acid (124 mg 0.96 mmol), N-hydroxysuccinimide (110 mg, 0.96 mmol), and DCC (200 mg, 0.97 mmol) was reacted with the free base of the compound (16) which was prepared by the compound (16) (635 mg, 0.96 mmol) and triethylamine (0.53 ml, 3.84 mmol) to give 497 mg (81.7%) of the compound (I-33).

$[\alpha]_D$ = -52.4° (c=0.508, MeOH, 23°C)
NMR(CD_3OD): 8.95 (1H, d, J=2.1 Hz), 7.44 (1H, d, J=2.1 Hz), 4.92 (1H, t, J=6.9 Hz), 4.49 (1H, dd, J=3.6, 8.5 Hz), 4.14 (3H, m), 3.97 (2H, s), 3.75 (1H, m), 3.40 (1H, m), 3.20 (2H, m), 2.4-1.8 (8H, m), 1.62 (2H, m), 1.32 (22H, m), 0.89 (3H, t, J=6.9 Hz).
Elemental analysis ($C_{32}H_{51}N_5O_6S$ $0.4H_2O$)

Calcd. :	C,59.96;	H,8.14;	N,10.92;	S,5.00.
Found :	C,59.97;	H,8.18;	N,11.02;	S,5.07.



Example 34- process 1

Preparation of benzyl cis-L-3-ethoxycarbonyl-5-methyl-2-oxo-oxazolidine-4-carboxylate (19)

[0058] A solution of cis-5-methyl-2-oxo-oxazolidine-4-carboxylic acid benzyl ester (706 mg, 3 mmol) which was synthesized in accordance with the method described in Chem. Lett., 1982, 1171 in tetrahydrofuran (12 ml) was cooled in a dry ice-acetone bath (-50 °C) under nitrogen atmosphere. To the solution was added potassium tert-butoxide (337 mg, 3 mmol) and the resulting mixture was stirred for 20 min. at the same temperature. To the mixture was added dropwise a solution of ethyl chlorocarbonate (0.46 ml, 4.83 mmol) in tetrahydrofuran (2 ml) over 10 min. The reaction mixture was stirred for 3h at -50 to -14 °C(bath temperature). The reaction mixture was partitioned between ice-water and ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and concentrated in vacuo. The residue was subjected to Lober® column (Merck inc.) and recrystallized from diethyl ether - hexane to give 847 mg of the compound (19) as colorless needle crystal.

Example 34- process 2

preparation of cis-L-3-ethoxycarbonyl-5-methyl-2-oxo-oxazolidine-4-carboxylic acid (20)

[0069] A solution of the compound (19) (718 mg, 2.34 mmol) in 50% aqueous methanol (3 ml) was hydrogenated using 5 % Pd/C (200 mg) for 2h at room temperature. The catalyst was filtered off and the filtrate was concentrated in vacuo to give 516 mg of compound (20) as powder.

Example 35- process 1

Preparation of benzyl cis-L-3-pivaloyloxymethyl-5-methyl-2-oxo-oxazolidine-4-carboxylate (21)

[0070] In a manner similar to that described in the method of Example 34-1, cis-L-5-methyl-2-oxo-oxazolidine-4-carboxylic acid benzyl ester (706 mg, 3 mmol) was pivaloyloxymethylatied with pivalic acid iodomethyl (1.19 g, 4.92 mmol) in the presence of potassium tert-butoxide (377 mg, 3 mmol) in tetrahydrofuran (12 ml) to give 893 mg of the compound (21) as colorless needle crystal.

Example 35- process 2

Preparation of benzyl cis-L-3-pivaloyloxymethyl-5-methyl-2-oxo-oxazolidine-4-carboxylic acid (22)

[0071] In a manner similar to that described in the method of Example 34-2, the compound (21) (892 mg, 2.55 mmol) was de-benzylesterificated by hydrogenating in the presence of 5 % Pd/C (250 mg) in aqueous methanol to give 642 mg of the compound (22) as colorless needle crystal.

Example 36- process 1

Preparation of cis-L-5-methyl-N-(4-morpholinylcarbonylmethyl)-2-oxo-oxazolidine-4-carboxylic acid benzyl ester (23)

[0072] In a manner similar to that described in the method of Example 34-1, to a solution of cis-L-5-methyl-2-oxo-oxazolidine-4-carboxylic acid benzyl ester (706 mg, 3 mmol) in THF (14 ml) was added potassium tert-butoxide (337 mg, 3 mmol) at - 53 °C in nitrogen atmosphere and the resulting mixture was stirred for 20 min. at the same temperature. To the reaction mixture was added a solution of N-iodoacetylmorpholine (1.15 g, 4.51 mmol) in THF (1 ml) and the resulting mixture was stirred for 4h at - 53 °C to -15 °C. The reaction mixture was partitioned between ethyl acetate and cooled sodium thiosulfate aq. The organic layer was washed with water, dried over magnesium sulfate, and concentrated in vacuo. The residue was subjected to Lobar® column (Merck inc.) and the fractions eluting with toluene : acetone = 5:1 were collected to yield the compound (23) (873 mg) as crystal.

Example 36- process 2

Preparation of cis-L-5-methyl-N-(4-morpholinylcarbonylmethyl)-2-oxo-oxazolidine-4-carboxylic acid (24)

[0073] In a manner similar to that described in the method of Example 34-2, the compound (23) (846 mg, 2.33 mmol) was de-benzylesterificated by hydrogenating in the presence of 5 % Pd/C (250 mg) in aqueous methanol to give 740 mg of the compound (24) as colorless needle crystal.

Example 37- process 1

Preparation of cis-L-5-methyl-N-(4-morpholinocarbonyl)-2-oxo-oxazolidine-4-carboxylic acid benzylester (25)

[0074] In a manner similar to that described in the method of Example 34-1, cis-L-5-methyl-2-oxo-oxazolidine-4-carboxylic acid benzyl ester (470 mg, 2 mmol) was reacted with 4-morpholine-carbonylchloride (0.38 ml, 3 mmol) in the presence of potassium tert-butoxide (224 mg, 2 mmol) in THF to give 630 mg of the compound (25).

Example 37- process 2

Preparation of cis-L-5-methyl-N-(4-morpholinocarbonyl)-2-oxo-oxazolidine-4-carboxylic acid (26)

[0075] In a manner similar to that described in the method of Example 34-2, the compound (25) (1.08 g, 3.10 mmol) was de-benzylesterificated by hydrogenating in the presence of 5 % Pd/C (200 mg) in aqueous methanol to give 706 mg of the compound (26).

Example 38- process 1

Preparation of cis-L-5-methyl-N-(4-oxo-butyl)-2-oxo-oxazolidine-4-carboxylic acid benzyl ester (27)

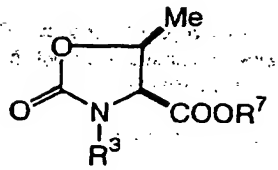
[0076] In a manner similar to that described in the method of Example 34-1, cis-L-5-methyl-2-oxo-oxazolidine-4-carboxylic acid benzyl ester (3 g, 12.9 mmol) was reacted with 1-iodo-2-butanone (3.83 g, 19.3 mmol) in the presence of potassium tert-butoxide (1.45 g, 12.9 mmol) in THF to give 2.15 g of the compound (27).

Example 38- process 2

Preparation of cis-L-5-methyl-N-(2-oxo-butyl)-2-oxo-oxazolidine-4-carboxylic acid (28)

[0077] In a manner similar to that described in the method of Example 34-2, the compound (27) (1.67 g, 5.47 mmol) was de-benzylesterificated by hydrogenating in the presence of 5 % Pd/C (480 mg) in aqueous methanol to give 0.65 g of the compound (28). The above results were shown in Tables 14 and 15.

Table 14



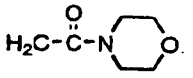
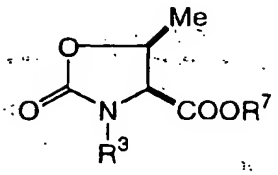
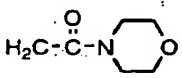
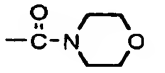
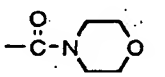
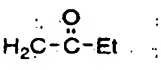
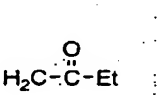
Example No.	Compound No.	R^3	R^7	$[\alpha]_D$	NMR
34-1	19	COOEt	Bzl	-63.1° (c=1.015, $CHCl_3$, 23°C)	($CDCl_3$): 7.37 (5H, bs), 5.29 (1H, d, J=12 Hz), 5.22 (1H, d, J=12 Hz), 4.79 (2H, m), 4.26 and 4.25 (2H, q, J=7.2 Hz), 1.30 (3H, d, J=6 Hz), 1.25 (3H, t, J=7.2 Hz).
34-2	20	COOEt	H		(DMSO-d_6): 4.93 (1H, m), 4.76 (1H, d, J=8.4 Hz), 4.21 (2H, m), 1.30 (3H, d, J=6.3 Hz), 1.22 (3H, t, J=7.2 Hz).
35-1	21	$CH_2OC(O)$-CMe_3	Bzl	-41.1° (c=1.003, $CHCl_3$, 22°C)	($CDCl_3$): 7.38 (5H, s), 5.43 (1H, d, J=11.2 Hz), 5.30 (1H, d, J=12 Hz), 5.24 (1H, d, J=11.2 Hz), 5.20 (1H, d, J=12 Hz), 4.79 (1H, m), 4.58 (1H, d, J=8.8 Hz), 1.23 (3H, d, J=6.4 Hz), 1.20 (9H, s).
35-2	22	$CH_2OC(O)$-CMe_3	H	-32.0° (c=1.007, MeOH, 22°C)	(DMSO-d_6): 5.31 (1H, d, J=11 Hz), 5.17 (1H, d, J=11 Hz), 4.89 (1H, dq, J=8.6, 6.8 Hz), 4.48 (1H, d, J=8.6 Hz), 1.26 (3H, d, J=6.8 Hz), 1.14 (9H, s).
36-1	23		Bzl	-112.1° (c=1.009, MeOH, 25°C)	($CDCl_3$): 7.38 (5H, s), 5.29 (1H, d, J=12 Hz), 5.15 (1H, d, J=12 Hz), 4.90 (2H, m), 4.55 (1H, d), 3.74 (1H, d) 3.3-3.7 (8H, m), 1.26 (3H, m)

Table 15



Example No.	Compound No.	R^3	R^7	$[\alpha]_D$	NMR
36-2	24		Bzl		($CDCl_3$): 5.01 (1H, dq, J=6.4, 9.0 Hz), 4.62 (1H, d, J=9 Hz), 4.46 (1H, d, J=17.2 Hz), 3.95 (1H, d, J=17.2 Hz), 3.4-3.8 (8H, m), 1.39 (3H, d, J=6.4 Hz)
37-1	25		Bzl	-68.4° (c=1.012, $CHCl_3$, 25°C)	($CDCl_3$): 7.37 (5H, s), 5.30 (1H, d, J=11.6 Hz), 5.15 (1H, d, J=11.6 Hz), 5.00 (1H, d, J=8.6 Hz), 4.89 (1H, m), 3.8-3.4 (8H, m), 1.26 (3H, d, J=6.4 Hz)
37-2	26		H	-48.8° (c=0.510, MeOH, 26°C)	(CD_3OD): 4.99 (1H, m), 4.87 (1H, d, J=6 Hz), 3.72 (4H, m), 3.54 (4H, m), 1.38 (3H, d, J=6.6 Hz)
38-1	27		Bzl	-129.5° (c=1.018, $CHCl_3$, 26°C)	($CDCl_3$): 7.37 (5H, s), 5.20 (2H, dd, J=11.6 Hz), 4.91 (1H, m), 4.73 (1H, d, J=9 Hz), 4.54 (1H, d, J=19.2 Hz), 3.79 (1H, d, J=19.2 Hz), 2.41 (2H, dq, J=2, 7.4 Hz), 1.06 (3H, t, J=7.4 Hz)
38-2	28		H	-110.3° (c=1.006, MeOH, 26°C)	($CDCl_3$): 4.98 (1H, m), 4.70 (1H, d, J=9 Hz), 4.52 (1H, d, J=18.8 Hz), 3.91 (1H, d, J=18.8 Hz), 2.47 (2H, q, J=7.4 Hz), 1.44 (3H, d, J=6.6 Hz), 1.09 (3H, t, J=7.4 Hz)

Example 34- process 3

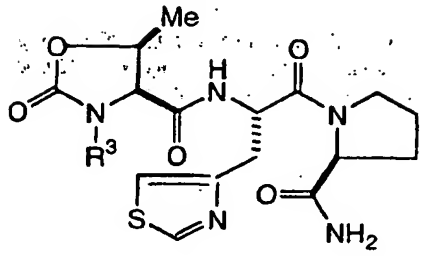
Preparation of cis-L-3-ethoxycarbonyl-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-prolineamide (I-34)

[0078] To the compound (20) (236 mg, 1.08 mmol) was added oxalyl chloride (0.15 ml, 1.72 mmol) and N, N-dimethylformamide (2 drops) and the resulting mixture was stirred for 2.5h. The reaction mixture was concentrated in vacuo. The residue was dissolved in tetrahydrofuran (3 ml) and to the solution was added a solution of 3-(4-thiazolyl)-L-alanyl-L-prolineamide (6,688 mg, 1.2 mmol) and triethylamine (0.61 ml, 4.35 mmol) in N, N-dimethylformamide (9 ml) under ice-cooling with stirring. The reaction mixture was stirred overnight at room temperature. After the percipitation was fil-

tered off, the filtrate was concentrated in vacuo. After the residue was dissolved in water and the solution was subjected to gel filtration column chromatography (MCI Gel CHP-20P, 200 ml, methanol-water) to give the crude compound (248 mg). The crude compound was subjected to silica gel column chromatography (chloroform : methanol = 9:1) to give 188 mg of the compound (I-34).

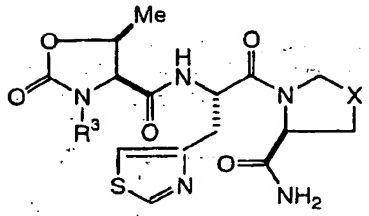
The compound (I-35) to (I-39) were synthesized in a manner similar to that described in the above method. The results were shown in Tables 16 and 17. When the compounds I-36, 38, and 39 were synthesized, DCC was used instead of oxalyl chloride as an activating agent.

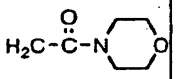
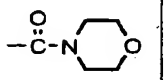
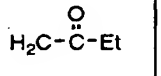
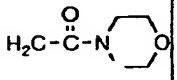
Table 16



Example No.	Compound No.	R^3	mp (°C)	$[\alpha]_D$	NMR
34-3	I-34	COOEt	126-130	-94.5° (c=0.511, H_2O, 23°C)	(CD_3OD): 8.97 and 8.96 (total 1H, d, J=2.1 Hz), 7.45 and 7.38 (total 1H, d, J=2.1 Hz), 5.01 (1H, t, J=6.9 Hz), 4.84 (1H, m), 4.78 (1H, d, J=8.4 Hz), 4.41 (1H, dd, J=4.2, 8.7 Hz), 4.20 (2H, q, J=7.2 Hz), 3.88 (1H, m), 3.48 (1H, m), 3.40 (1H, dd, J=6.9, 14.7 Hz), 3.20 (1H, dd, J=7.2, 14.7 Hz), 2.19 (1H, m), 1.99 (3H, m), 1.37 and 1.30 (total 3H, d, J=6.3 Hz), 1.25 and 1.20 (total 3H, t, J=7.2 Hz).
35-3	I-35	$CH_2OC(O)$-CMe_3	212-213	-66.3° (c=0.514, MeOH, 22.5°C)	(CD_3OD): 8.97 and 8.94 (total 1H, d, J=2.1 Hz), 7.48 and 7.40 (total 1H, d, J=2.1 Hz), 5.33 and 5.31 (total 1H, d, J=11.1 Hz), 5.03 (1H, t, J=6.9 Hz), 5.01 and 4.96 (total 1H, d, J=11.1 Hz), 4.84 (1H, m), 4.58 and 4.54 (total 1H, d, J=8.7 Hz), 4.41 and 4.32 (1H, dd, J=3.9, 8.1 Hz), 3.89 (1H, m), 3.52 (1H, m), 3.41 (1H, dd, J=6.6, 14.7 Hz), 3.22 (total 1H, dd, J=7.2, 14.7 Hz), 2.29 (1H, m), 2.00 (3H, m), 1.30 and 1.25 (total 3H, d, J=6.6 Hz), 1.21 and 1.96 (total 9H, s).

Table 17



Example No.	Compound No.	R^3	X	$[\alpha]_D$	NMR
36-3	I-36		CH_2	-79.1° (c=1.004, H_2O, 25°C)	(CD_3OD): 8.98 and 8.96 (total 1H, d, J=2 Hz), 7.46 and 7.37 (total 1H, d, J=2 Hz),4.9-5.1 (2H, m), 4.53 and 4.52 (total 1H, d, J=9 Hz), 4.40 (1H, m), 4,36 (1H, d, J17.2 Hz), 3.86 (1H, m), 3,86 (1H, d, J17.2 Hz), 3.3-3.7 (10H, m), 3.18(1H, dd, J=7.8, 14.4 Hz), 1.8-2.3 (4H, m), 12.4 and 1.17 (total 3H, d, J=6.4 Hz)
37-3	I-37		CH_2	-69.7° (c=0.505, MeOH, 26°C)	(CD_3OD): 8.93 and 8.72 (total 1H, d, J=1.8 Hz), 7.48 and 7.39 (total 1H, d, J=1.8 Hz), 4.9-5.1 (3H, m), 4.42 (1H, dd, J= 4.4, 8.4 Hz), 3.85 (1H, m), 3.70 (4H, m), 3.50 (4H, m), 1.8-2.3 (4H, m) 1.28 (3H, d, J=5.8 Hz)
38-3	I-38		CH_2	-80.4° (c=1.012, MeOH, 26°C)	(CD_3OD): 8.96 and 8.98 (total 1H, d, J=2.1 Hz), 7.35 and 7.43 (total 1H, d, J=2.1 Hz), 5.02 (1H, dd, J=6.6 Hz), 4.92 (1H, m), 4.48 and 4.49 (toal 1H, d, J=4.4, 8.4 Hz), 4.40 (1H, dd, J=4.2, 8.4 Hz), 4.34 (1H, d, J=18.6 Hz), 3.76 (1H, d, J=18.6 Hz), 3.85 (1H, m), 3.51 (1H, m), 3.38 (1H, dd, J=6.6, 14.9 Hz), 3.17 (1H, dd, J=6.6, 14.9 Hz), 2.48 (2H, m), 1.80-2.30 (4H, m), 1.26 (3H, d, J=6.9 Hz), 1.21 (3H, d, J=6.9 Hz), 1.06 (3H, t, J=7.8 Hz), 1.05 (3H, t, J=4.8 Hz)
39-3	I-39		S	-103.9° (c=1.004, H_2O, 25°C)	(CD_3OD): 8.97 (1H, d,J=2 Hz), 7.47 and 7.42 (total 1H, d, J=2 Hz), 4.8-5.2 (4H, m), 4.4-4.62 (4H, m), 437(1H, d, J=17.2 Hz), 3.86 (1H, d, J17.2 Hz), 3.67 (4H, m), 3.50 (4H, m), 3.1-3.4 (4H, m), 1.19 (3H, d, J=6.6 Hz)

Example 40

Preparation of cis-L-3-morpholinomethyl-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-prolineamide (I-40)

[0079] To a ethanol (3.6 ml) solution of the compound (I-10) (237 mg, 0.6 mmol) was added morpholine (180 mg, 2.07 mmol) and 37 % formalin (0.22 ml) and the resulting mixture was stirred for 3h on oil bath (60 °C). The reaction mixture was concentrated in vacuo. The residue was dissolved in a mixed solvents of chloroform and methanol and the solution was subjected to alumina column chromatography (chloroform : methanol = 97:3) to give the fractions containing the aimed compound (258 mg). The fractions were dissolved in methanol and a large amount of diethyl ether was added to the solution. The precipitation which appeared was filtered off to give 195 mg of the compound (I-40).

[0080] The compound (I-41) was synthesized in a manner similar to that described in the above method. The results were shown in Table 18.

Example 42

Preparation of cis-L-3-(N-methylpiperazinyl)methyl-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-prolineamide hydrochrolide (I-43)

[0081]

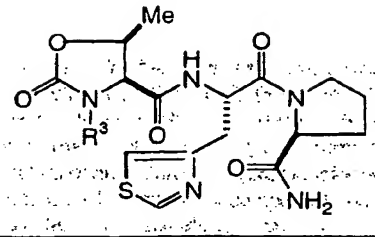
i) In a manner similar to that described in the method of Example 40, the compound (I-10) (395 mg, 1 mmol) was treated with N-methylpiperazine (0.2 ml, 2.34 mmol) and 37 % formalin (0.24 ml) in ethanol (10 ml) to form Mannich base, giving 350 mg of the compound (I-42) which was free base of the compound (I-43). The detailed date was shown in Table 18.

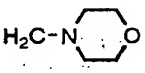
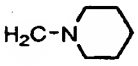
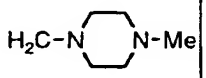
ii) After the compound (I-42) (120 mg, 0.244 mmol) was dissolved in methanol (1 ml), to this solution was added a solution 4N hydrogen chloride in ethyl acetate (0.15 ml). Subsequently, to the mixture was added diethyl ether and the precipitation which appeared was filtered off to give 138 mg of the compound (I-43).

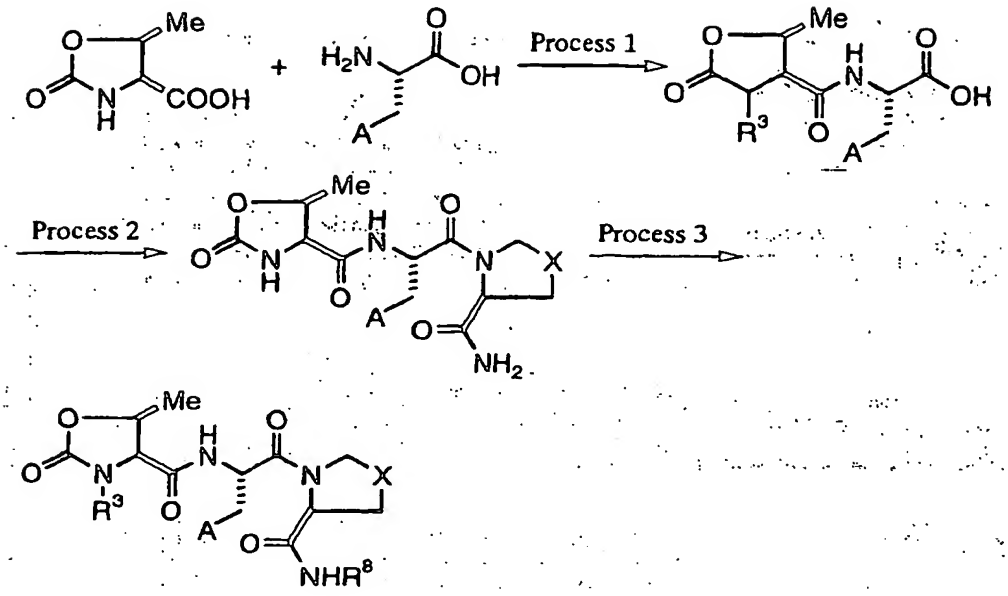
$[\alpha]_D$ = -82° (c=0.51, H_2O, 23°C)
IR(KBr)cm^{-1} : 3412, 1764, 1677, 1647, 1544, 1446, 1342, 1298, 1221.
Elemental analysis ($C_{22}H_{32}N_6O_5S$ 1.8HCl 0.3Et_2O 1.2H_2O)

Calcd. :	C,46.28;	H,6.56;	N,13.96;	Cl,10.60;	S,5.33.
Found :	C,46.08;	H,6.38;	N,14.27;	Cl,10.88;	S,5.37.

Table 18



Example No.	Compound No.	R^3	$[\alpha]_D$	NMR
40	I-40		-61° (c=0.503, H_2O, 23.5°C)	(CD_3OD): 8.98 and 8.96 (total 1H, d, J=1.8 Hz), 7.43 and 7.36 (total 1H, d, J=1.8 Hz), 5.08 (1H, dd, J=6.0, 7.8 Hz), 4.84 (1H, m), 4.46 (1H, d, J=8.4 Hz), 4.42 (1H, dd, J=3.9, 8.4 Hz), 4.07 (1H, d, J=12.6 Hz), 3.91 (1H, m), 3.63 (5H, m), 3.56 (1H, d, J=12.6 Hz), 3.41 (1H, dd, J=6.0, 14.4 Hz), 3.19 (1H, dd, J=7.8, 14.4 Hz), 2.47 (4H, m), 2.21 (1H, m), 2.01 (2H, m), 1.30 and 1.24 (total 3H, d, J=6.9 Hz).
41	I-41		-69.1° (c=0.966, H_2O, 23.5°C)	(CD_3OD): 8.98 and 8.96 (total 1H, d, J=2 Hz), 7.43 and 7.36 (total 1H, d, J=2 Hz), 5.07 (1H, dd, J=6.4, 8.2 Hz), 4.80 (1H, m), 4.44 (1H, d, J=8.6 Hz), 4.41 (1H, dd, J=48.2 Hz), 4.11 and 4.10 (total 1H, d, J=13 Hz), 3.90 (1H, m), 3.56 (5H, d, J=13 Hz), 3.51 (1H, m), 3.40 (1H, dd, J=6.4, 14.4 Hz), 2.3-2.6 (8H, m), 2.27 and 2.15 (total 3H, s), 2.20 (1H, m), 2.01 (2H, m), 1.29 and 1.24 (total 3H, d, J=6.2 Hz)
42	I-42		-62.3° (c=0.514, H_2O, 23.5°C)	(DMSO-d_6): 9.06 and 9.02 (total 1H, d, J=2 Hz), 8.81 and 8.59 (total 1H, d, J=8 Hz), 7.43 (1H, d, J=2 Hz), 7.34 (1H, br. s), 7.16 and 6.90 (1H, br.s), 4.96 (1H, m), 4.74 (1H, m), 4.50 and 4.37 (total 1H, d, J=8.2 Hz), 4.22 (1H, m), 3.95 (1H, d, J=12.8 Hz), 3.72 (1H, m), 3.60 (1H, m), 3.26 (1H, d, J=12.8 Hz), 3.20 (1H, dd, J=5.14 Hz), 3.04 (1H, dd, J=9.8, 14 Hz), 2.31 (4H, m), 1.6-2.1 (4H, m), 1.40 (6H, m), 1.16 and 1.09 (total 3H, d, J=6.4 Hz).



Example 44 and 45 - process 1

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanine (29)

[0082] A solution of cis-L-5-methyl-2-oxo-oxazolidine-4-carboxylic acid (1.08 g, 7.5 mmol) in N, N-dimethylformamide (30 ml) was added N-hydroxysuccinimide (650 mg, 8.25 mmol) and DCC (1.70 g, 8.25 mmol) and the resulting mixture was stirred for 3h at room temperature. After the precipitation which appeared was filtered off, to the filtrate was added 3-(4-thiazolyl)-L-alanine trifluoroacetate (4.64 g, 7.5 mmol) and triethylamine (5.23 ml, 37.5 mmol). The reaction mixture was stirred for 16h at room temperature. The reaction mixture was concentrated in vacuo. The residue was subjected to gel filtration column chromatography (MCI GEL CHP-20P, 200 ml, aq. MeOH) and to silica gel column chromatography (chloroform : methanol = 10:1) to give 890 mg (39.7 %) of the compound (29).

NMR(CD_3OD): 9.02 (1H, d, J=1.8 Hz), 8.46 (1H, d, J=7.8 Hz), 7.74 (1H, s), 7.38 (1H, d, J=1.8 Hz), 4.77 (1H, dq, J=8.7, 6.6 Hz), 4.66 (1H, m), 4.21 (1H, d J=8.7 Hz), 3.24 (1H, dd, J=5.1, 15 Hz), 3.13 (1H, dd, J=8.4, 15 Hz), 1.13 (3H, d, J=6.6 Hz).
Elemental analysis ($C_{11}H_{13}N_3O_5S$ $0.2H_2O$)

Calcd. :	C,43.62;	H,4.46;	N,13.87;	S,10.59.
Found :	C,43.66;	H,4.45;	N,13.73;	S,10.39.

Example 44 and 45 - process 2

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-prolineamide (I-10)

[0083] To a solution of the compound (29) (150 mg, 0.5 mmol) and N-hydroxysuccinimide (63 mg, 0.55 mmol) in N, N-dimethylformamide (5 ml) was added DCC (114 mg, 0.55 mmol) under ice-cooling and the resulting mixture was stirred for 60 min. Subsequently, to the mixture was added L-prolineamide (63 mg, 0.55 mmol) and the resulting mixture

was stirred for additional 16h at room temperature. After the precipitation which appeared was filtered off, the filtrate was concentrated in vacuo. The residue was dissolved in water and was subjected to gel filtration column chromatography (MCL GEL CHP-20P, 200 ml, aq. MeOH) to give 164 mg (82.8 %) of the same compound which are synthesized in Example 10-3.

Example 44 and 45 - process 3

Preparation of cis-L-3-acetoxymethyl-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-N-(acetoxymethyl)-L-prolineamide (I-44) and cis-L-3-acetoxymethyl-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-prolineamide (I-45)

[0084] A solution of the compound (I-10) (198 mg, 0.5 mmol) in ethanol (1 ml) was added 0.1 ml of the solution of triethylamine (0.5 ml) in ethanol (10 ml) and 37 % formalin (0.13 ml, 1.6 mmol) and the resulting mixture was heated at reflux on oil bath (105 °C) for 2h. The reaction mixture was concentrated in vacuo. After the residue was dissolved in pyridine (9 ml), to the mixture was added acetic anhydride (0.9 ml) and was stood for 1h at room temperature. After toluene was added to the reaction mixture, the resulting mixture was concentrated in vacuo. The residue was subjected to silica gel column chromatography (chloroform : methanol = 19:1) to give 143 mg of the compound (I-44) and 71 mg of the compound (I-45).

Example 46

Preparation of cis-L-3-acetyl-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)L-alanyl-L-prolineamide (I-46)

[0085] After the compound (I-10) (125 mg, 0.316 mmol) was dissolved in pyridine (5 ml), to the mixture was added acetic anhydride (0.6 ml) and the resulting mixture was stood for 16 h at room temperature. Additionally, to the mixture was added acetic anhydride (0.6 ml) and the resulting mixture was stood for 2 days at room temperature. After toluene was added to the reaction mixture, the mixture was concentrated in vacuo. The residue was subjected to silica gel column chromatography (chloroform : methanol = 19:1) to give 94 mg of the compound (I-46).

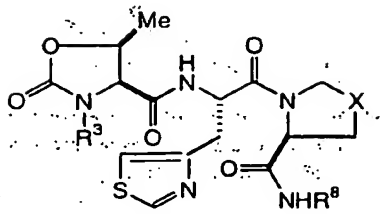
Example 47

Preparation of cis-L-3-acetoxy-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-thaiazolidine-4-carboxyamide (I-47)

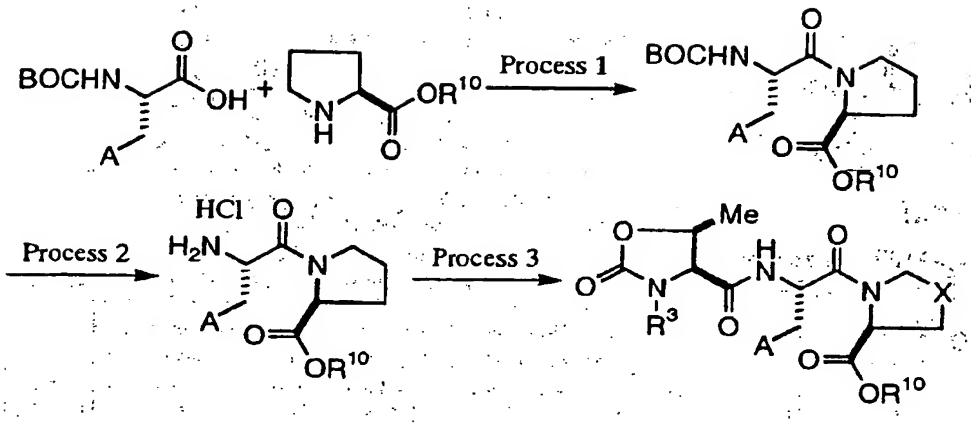
[0086] In a manner similar to that described in the method of Example 44 and 45 - 3, after the compound (I-11) (210 mg, 0.5 mmol) was hydroxymethylated by treating with 37 % formalin (0.13 ml) and triethylamine (0.05 ml), the resulting compound was acetylated by treating with acetic anhydride - pyridine to give 140 mg of the compound (I-47).

The above results were shown in Table 19.

Table 19



Example No.	Compound No.	R^3	R^8	X	NMR
44-3	I-44	CH_2OAc	CH_2OAc	CH_2	($CDCl_3$): 9.02 and 8.97 (total 1H, d, J=2.1 Hz), 7.47 and 7.36 (1H, d, J=2.1 Hz). 5.31 (1H, d, J=11.4 Hz) 5.24 (1H, d, J=10.2 Hz), 5.20 (1H, d, J=10.2 Hz), 5.01 (1H, d, J=11.4 Hz), 5.00 (1H, t, J=6.9 Hz), 4.80 (1H, m), 4.57 and 4.55 (total 1H, d, J=8.4 Hz), 4.31 (1H, dd, J=4.2, 8.4 Hz), 3.86 (1H, m), 3,42 (1H, m), 3,35 (1H, m), 3,20 (1H, dd, J=6.9, 14.7 Hz), 1.8-2.3 (4H, m), 2.05 (3H, s), 2.04 (3H, s), 1.29 and 1.24 (total 3H, d, J=6.6 Hz).
45-3	I-45	CH_2OAc	H	CH_2	(CD_3OD): 8.97 and 8.94 (1H, d, J=1.8 Hz), 7.47 and 7.39 (total 1H, d, J=1.8 Hz), 5.31 amd 5.29 (total 1H, d, J=11.2 Hz), 5.04 (1H, t, J=6.9 Hz), 5.01 and 4.98 (total 1H, d, J=11.1 Hz), 4.80 (1H, m), 4.59 and 4.56 (1H, d, J=8.7 Hz), 4.41 and 4.30 (1H, dd, J=3.9, 8.4 Hz), 3.87 (1H, m), 3.60 (1H, m), 3.40 (1H, dd, J=14.1, 6.6 Hz), 3.22 (1H, dd, J=6.9, 14.1 Hz), 1.7-2.3 (4H, m), 2.05 (3H, s), 1.30 and 1.24 (total 3H, d, J=6.6 Hz).
46	I-46	Ac	H	CH_2	(CD_3OD): 8.94 and 8.93 (total 1H, d, J=1.8 Hz), 7.47 and 7.38 (total 1H, d, J=1.8 Hz), 4.97 (1H, t, J6.9 Hz), 4.8-4.9 (2H, m), 4.41 and 4.25 (total 1H, dd, J=3.9, 8.7 Hz), 3.85 (1H, m), 3.44 (1H, m), 3,39 (1H, dd, J=7.2, 15 Hz), 3.23 (1H, dd, J=6.9, 15 hz), 2.46 (3H, s), 1.8-2.3 (4H, m), 1.2-1.4 (3H, m).
47	I-47	CH_2OAc	H	S	(CD_3OD): 8.94 and 8.99 (total 1H, d, J=2.1 Hz). 7.42 and 7.48 (total 1H, d, J=2.1 Hz), 5.32 (1H, d, J=11.4 Hz), 5.13 (1H, t, J=6.9 Hz), 5.09 (1H, d, J=8.7 Hz), 5.03 (1H, d, J=11.4 Hz), 4.70-4.90 (2H, m), 4.57 (1H, d, J=8.7 Hz), 4.48 (1H, d, J=8.7 Hz). 3,43 (1H, dd, J=6.9, 14.4 Hz), 3.10-3.40 (3H, m), 2.05 (3H, s). 1.25 and 1.32 (total 3H, d, J=6.6 Hz)



Example 48 - process 1

Preparation of N-(tert-butyloxycarbonyl)-3-(4-thiazolyl)-L-alanyl-L-proline benzyl ester (30)

[0087] A solution of N-(tert-butyloxycarbonyl)-3-(4-thiazolyl)-L-alanine (2.72 g, 10 mmol), L-proline benzyl ester hydrochloric acid (2.42 g, 10 mmol), and HOBT (135 mg, 1 mmol) in tetrahydrofuran (60 ml) was added triethylamine (1.4 ml, 10 mmol) and DCC (2.43 g, 11.8 mmol) and the resulting mixture was stirred for 18 h at room temperature. After the precipitation which appeared was filtered off, the filtrate was concentrated in vacuo. The residue (5.5 g) was subjected to silica gel column chromatography with Lobar® column C (Merck inc.) (toluene : acetone = 9:1) to give 4.16 g of the compound (30).

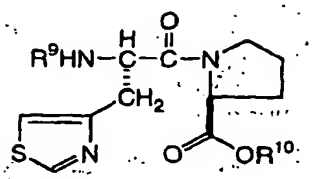
Example 48 - process 2

Preparation of 3-(4-thiazolyl)-L-alanyl-L-proline benzyl ester hydrochloride (32)

[0088] To a solution of the compound (30) (3 g, 6.528 mmol) in ethyl acetate (10 ml) was added a solution of 4N hydrogen chloride in ethyl acetate (33 ml) under ice-cooling and the resulting mixture was stirred for 3h. To the reaction mixture was added diethyl ether and the precipitation which appeared was filtered off to give 2.77 g of compound (32). This compound was used in the next reaction without purification.

The compounds (31) and (33) are synthesized in a manner similar to that described in the above method. The results were shown in Table 20.

Table 20



Example No.	Compound No.	R^9	R^{10}	salt	$[\alpha]_D$	NMR
48-1	30	BOC	Bzl	-	-55.6° (c=1.03, MeOH, 23°C)	($CDCl_3$): 8.75 and 8.72 (total 1H, d, J=1.8 Hz), 7.35 (5H, m, Ph), 7.10 and 7.08 (total 1H, d, J=1.8 Hz), 5.39 (1H, d, J=9 Hz), 5.19 (1H, d, J=12.4 Hz), 5.27 (1H, d, J=12.3 Hz), 4.81 (1H, m), 4.58 (1H, dd, J=3.9, 8.4 Hz), 3.73 and 3.51 (total 2H, m), 3.26 (1H, dd, J=5.7 Hz, 14.1 Hz), 3.02 (1H, dd, J=7.5, 14.1 Hz), 2.19 (1H, m), 1.97 (3H, m), 1.37 (9H, s).
48-2	32	H	Bzl	HCl		(CD_3OD): 9.41 (1H, d, J=1.8 Hz), 7.68 (1H, d, J=1.8 Hz), 5.17 (1H, s), 4.60 (2H, m), 3.75 (1H, m), 3.45 (3H, m), 2.30 (1H, m), 2.00 (3H, m).
49-1	31	BOC	iso-Pr	-	-40.8° (c=1.015, $CHCl_3$, 26°C)	($CDCl_3$): 8.77 (1H, d, J=2 Hz), 7.19 (1H, s), 5.40 (1H, d, J=8.6 Hz), 5.03 (1H, q, J=6.2 Hz), 4.83 (1H, m), 4.48 (1H, m), 3.73 (1H, m), 3.59 (1H, m), 3.32 (1H, dd, J=5.2 Hz, 14.4 Hz), 3.04 (1H, dd, J=7.8, 14.4 Hz), 2.20 (1H, m), 1.97 (3H, m), 1.36 (9H, s), 1.26 (3H, d, J=6.4 Hz), 1.22 (3H, d, J=6.4 Hz).
49-2	33	H	iso-Pr	HCl		

Example 48 - process 3

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-proline benzyl ester (I-48)

[0089] A solution of cis-L-5-methyl-2-oxo-oxazoline-4-carboxylic acid (316 mg, 2.17 mmol) and N-hydroxysuccinimide (249 mg, 2.17 mmol) in N, N-dimethylformamide (5 ml) was added DCC (448 mg, 2.17 mmol) and the resulting mixture was stirred for 4h at room temperature. After the precipitation which appeared was filtered off, to the filtrate was added 865 mg (2.17 mmol) of the compound (32) and triethylamine (1.21 ml, 8.7 mmol). The reaction mixture was stirred for 16h at room temperature. After the precipitation which appeared was filtered off, the filtrate was concentrated in vacuo.

The residue was subjected to gel filtration column chromatography (MCL GEL CHP-20P, 200 ml, aq. MeOH) and to silica gel column chromatography to give 496 mg of the compound (I-48).

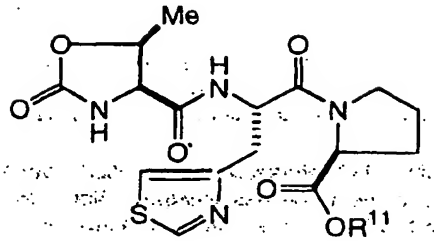
[0090] The compound (I-49) was synthesized in a manner similar to that described in the above method. The results were shown in Table 21.

Example 50

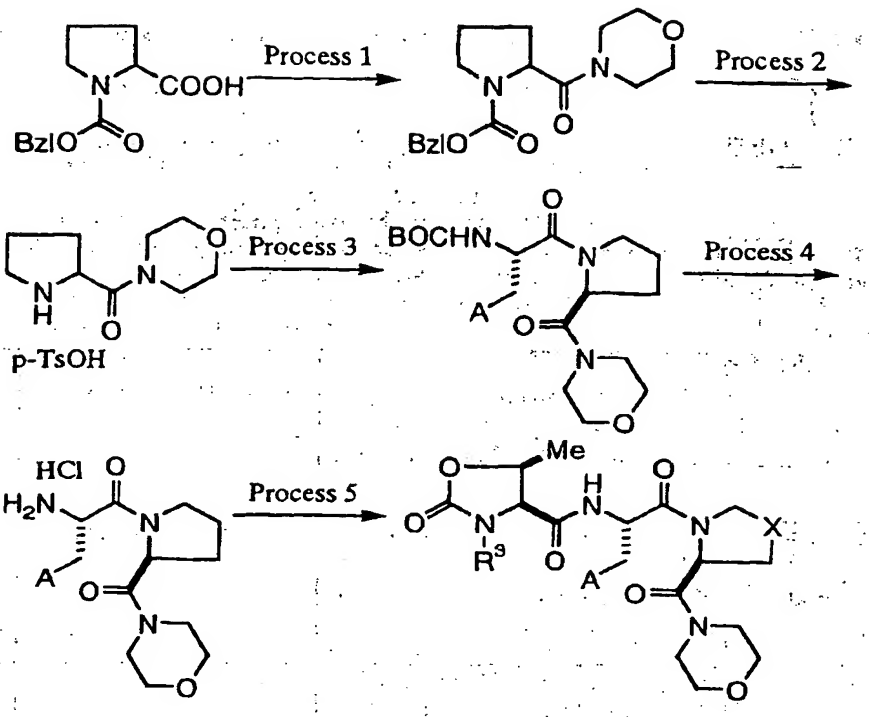
Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-proline(I-50)

[0091] A solution of the compound (I-48) (1.99 g, 4.09 mmol) in 50 % aqueous methanol was added lithium hydroxide (858 mg, 20.45 mmol) and the resulting mixture was stirred for 35 min. at room temperature. After the reaction mixture was neutralized by adding 1N hydrochloric acid (20.4 ml), the resulting mixture was concentrated in vacuo to about half volume. The aqueous solution was washed with ethyl acetate twice. The aqueous layer was subjected to gel filtration column chromatography (MCI GEL CHP-20P, 200 ml, aq. MeOH) to give 1.29 g of the compound (I-50). The result was shown in Table 21.

Table 21



Example No.	Compound No.	R^{11}	$[\alpha]_D$	IR(cm^{-1})	NMR
48-3	I-48	Bzl	-55.9° (c=0.508, MeOH, 26°C)		(CD_3OD): 8.93 (1H, d, J=2 Hz), 7.35 (5H, m, Ph), 7.30 (1H, d, J=2 Hz), 5.15 (12H, s), 5.11 (1H, m), 4.90 (1H, m), 4.49 (1H, m), 4.31 (1H, d, J=8.6 Hz), 3.90 (1H, m), 3.60 (1H, m), 3.17 (2H, m), 2.25 (1H, m), 1.97 (3H, m), 1.17 (3H, d, J=6.6 Hz).
49-3	I-49	iso-Pr	-53.7° (c=0.501, MeOH, 25°C)		(CD_3OD): 8.99 (1H, d, J=2 Hz), 7.44 (1H, d, J=2 Hz), 5.00 (3H, m), 4.40 (1H, m), 4.34 (1H, d, J=8.6 Hz), 3.93 (1H, m), 3.66 (1H, m), 2.30 (1H, m), 2.00 (3H, m), 1.28 (6H, t, J=6.2 Hz), 1.20 (3H, d, J=6.6 Hz).
50	I-50	H	-52.0° (c=1.01, H_2O, 23°C)	(KBr) 3398,3299, 1749,1636, 1523,1450, 1230.	(CD_3OD): 8.95 (1H, d, J=2.1 Hz), 7.40 and 7.33 (total 1H, d, J=2.1 Hz), 5.09 (1H, dd, J=5.4, 8.4 Hz), 4.90 (1H, m), 4.42 (1H, dd, J=3.6, 8.1 Hz), 4.37 and 4.32 (total 1H, d, J=8.7 Hz), 3.91 (1H, m), 3.61 (1H, m), 3.30 (1H, m), 3.17 (1H, dd, J=8.4, 14.7 Hz), 2.25 (1H, m), 2.01 and 1.83 (total 3H, m), 1.25 and 1.18 (total 3H, d, J=6.9 Hz).



Example 51 - process 1

Preparation of 4-(N-benzyloxycarbonyl-L-prolyl)morpholine (34)

[0092] A solution of N-benzyloxycarbonyl-L-proline (5 g, 20.06 mmol), morpholine (1.92 ml, 20.06 mmol), arid N-hydroxysuccinimide (2.31 g, 20.06 mmol) in N, N-dimethylformamide (100 ml) was added DCC (4.14 g, 20.06 mmol) and the resulting mixture was stirred for 4h at room temperature. After the precipitation was filtered off, the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate and the resulting precipitation was filtered off. After the filtrate was washed with dilute hydrochloric acid, saturated sodium hydrogencarbonate aq., and water, the organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was crystallized from the mixed solvents of ethyl acetate - hexane to give the compound (34) (4.44 g, 69.5 %).

mp : 142 - 143°C
$[\alpha]_D$=-18.0° (c=1, $CHCl_3$, 23°C)
IR($CHCl_3$)cm-1: 1700, 1660, 1420.
NMR($CDCl_3$): 7.35 (5H, m), 5.12 (2H, m), 4.59 and 4.70 (total 1H, dd, J=3.6, 8.4 Hz), 3.20-3.90 (10H, m), 1.80-2.30 (4H, m).
Elemental analysis ($C_{17}H_{22}N_2O_4$)

Calcd. :	C,64.13;	H,6.96;	N,8.80.
Found :	C,53.99;	H,6.94;	N,8.81.

Example 51 - process 2

Preparation of 4-L-prolyl-morpholine p-toluensulfonate (35)

[0093] A solution of the compound (35) (3.6 g, 11.31 mmol) in methanol (50 ml) - water (10 ml) was hydrogenated using 5 % Pd/C (1.6 g) and p-toluenesulfonic acid (2.15 g, 11.31 mmol) for 3h at room temperature. The catalyst was filtered off and the filtrate was concentrated in vacuo to obtain the compound (35) (4.31 g, 100 %):

mp: 130 - 131°C
NMR(CD_3OD) : 7.70 (2H, m), 7.24 (2H, m), 4.65 (1H, dd, J=6.2, 8.4 Hz), 3.20-3.80 (10H, m), 1.80-2.60 (4H, m), 2.37 (3H, s).
Elemental analysis ($C_{16}H_{24}N_2O_5S$)

Calcd. :	C,53.92;	H,6.79;	N,7.86;	S,9.00.
Found :	C,53.91;	H,6.73;	N,7.97;	S,8.99.

Example 51 - process 3

Preparation of 4-[N-[N-(tert-butoxycarbonyl)-3-(4-theiazolyl)-L-alanyl]-L-prolyl]morpholine (36)

[0094] In a manner similar to that described in the method of synthesis of the compound (34), the compound (35) (2.7 g, 7.57 mmol) was condensed with N-(tert-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine (2.03 g, 7.57 mmol) in the presence of HOBT (200 mg, 1.498 mmol), triethylamine (2.1 ml, 14.98 mmol), and DCC (1.55 g, 7.49 mmol) in N, N-dimethylformamide. The product was subjected to silica gel column chromatography (chloroform : methanol = 50:1) to give the compound (36) (2.23 g, 67.1%).

$[\alpha]_D$ = -23.1° (c=0.91, $CHCl_3$, 25°C)
IR($CHCl_3$)cm^{-1}: 3433, 1707, 1644, 1501, 1441, 1232, 1167, 1115.
NMR($CDCl_3$) : 8.76 (1H, d, J=2 Hz), 7.21 (1H, d, J=2 Hz), 5.46 (1H, d J=9 Hz), 4.83 (2H, m), 3.40-4.00 (10H, m), 3.35 (1H, dd, J=5, 14.6 Hz), 3.08 (1H, dd, J=7.8, 14.6 Hz), 1.70-2.30 (4H, m), 1.37 (9H, s).
Elemental analysis ($C_{20}H_{30}N_4O_5S$ 0.5H_2O)

Calcd. :	C,53.67;	H,6.98;	N,12.52;	S,7.16.
Found :	C,53.71;	H,7.07;	N,12.34;	S,7.17.

Example 51 - process 4

Preparation of 4-[N-[3-(4-thiazolyl)-L-alanyl]-L-prolyl]morpholine hydrochloride (37)

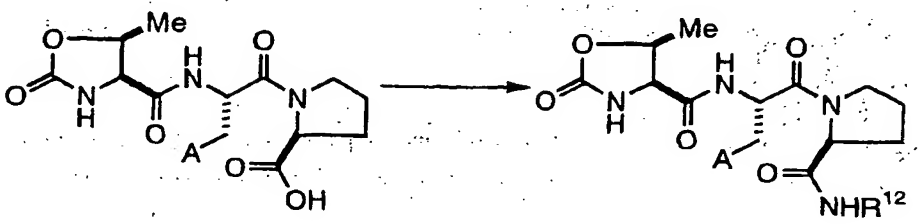
[0095] To a solution of the compound (36) (1.5 g, 3.42 mmol) in ethyl acetate (17 ml) was added a solution of 4N hydrochloric acid in ethyl acetate (17 ml) under ice-cooling and the resulting mixture was stirred for 3h at the same temperature with stirring. The precipitation which appeared was filtered off and washed with ethyl acetate to give the compound (37) (1.33 g, 94.4 %).

$[\alpha]_D$ = -39.1° (c=1, MeOH, 25°C)
IR($CHCl_3$)cm^{-1} : 3429, 1741, 1654, 1610, 1465, 1370, 1238, 1111.
NMR(CD_3OD) : 9.86 (1H, d, J=2 Hz), 8.06 (1H, d, J=2 Hz), 4.98 (1H, dd, J=6.0, 8.4 Hz), 4.76 (1H, t, J=5.4 Hz), 3.40-4.00 (12H, m), 1.80-2.40 (4H, m).

Example 51 - process 5

Preparation of 4-[N-[N-(cis-L-5-methyl-2-oxo-oaxzolidine-4-yl-carbonyl)-3-(4-thiazolyl)-L-alanyl]-L-prolyl]morpholine (I-51)

[0096] In a manner similar to that described in the method of synthesis of the compound (34), cis-L-5-methyl-2-oxo-oxazolidine-4-carboxylic acid (300 mg, 2.07 mmol) was condensed with the compound (37) (850 mg, 2.07 mmol) in the presence of N-hydroxysuccinimide (240 mg, 2.07 mmol), DCC (470 mg, 2.28 mmol), and triethylamine (1.16 ml, 8.28 mmol) in N, N-dimethylformamide to give 560 mg of the compound (I-51). The result was shown in Table 22.



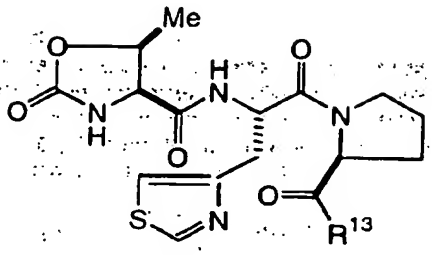
Example 52

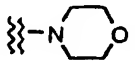
Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-N-(tert-butyl)-L-prolineamide (I-52)

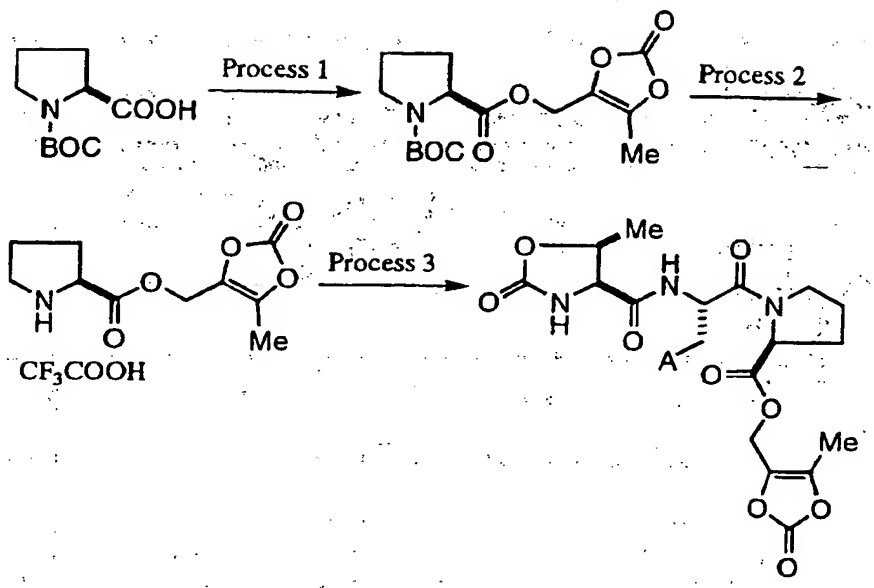
[0097] In a manner similar to that described in the method of synthesis of the compound (34), the compound (I-50) (300 mg, 0.76 mmol) was condensed with tert-butylamine (110 mg, 1.52 mmol) in the presence of N-hydroxysuccinimide (87 mg, 0.76 mmol) and DCC (170 mg, 0.84 mmol) in N, N-dimethylformamide to give 210 mg of the compound (I-52).

[0098] In the manner to that described in the above method, the compound (I-53) was synthesized. The above results were shown in Table 22.

Table 22



Example No.	Compound No.	R^{13}	$[\alpha]_D$	NMR
51-5	I-51		-55.9° (c=0.508, MeOH, 26°C)	(CD3OD): 8.94 and 8.98 (total 1H, d, J2 Hz), 7.32 and 7.42 (total 1H, d, J=2 Hz), 5.09 (1H, dd, J=4.6, 9.4 Hz), 4.70-5.00 (2H, m), 4.30 and 4.33 (total 1H, d, J=8.6 Hz), 3.50-4.10 (10H, m), 3.38 (1H, dd, J=4.6, 15 Hz), 3.15 (1H, dd, J=9.4, 15 Hz), 1.60-2.40 (4H, m), 1.17 and 1.21 (total 3H, d, J=6.6 Hz).
52	I-52	t-BuNH	-53.7° (c=0.501, MeOH, 25°C)	(CD_3OD): 8.95 and 8.97 (total 1H, d, J=1.8 Hz), 7.57 and 7.71 (total 1H, s), 7.34 and 7.42 (total 1H, d, J=1.8 Hz), 5.06 (1H, dd, J=5.4, 8.1 Hz), 4.90 (1H, m), 4.34 (1H, t, J=8.7 Hz), 4.31 (1H, d, J=8.7 Hz), 3.60-3.91 (2H, m), 3.37 (1H dd, J=5.4, 15.3 Hz), 3.19 (1H, dd, J=8.1, 15.3 Hz), 1.70-2.30 (4H, m), 1.33 (9H, s), 1.18 and 1.25 (total 3H, d, J6.3 Hz).
53	I-53	n-PenNH	-52.0° (c=1.01, H_2O, 23°C)	(CD_3OD): 8.97 (1H, d, J=2.1 Hz), 7.35 and 7.44 (total 1H, d, J=2.1 Hz), 5.00 (1H, t, J=6.9 Hz), 4.91 (1H, m), 4.37 (1H, dd, J=4.2, 10.5 Hz), 4.33 and 4.35 (total 1H, d, J=9 Hz), 3.87 (1H, m), 3.30-3.60 (5H, m), 1.70-2.30 (4H, m), 1.51 (2H, m), 1.31 (4H, m), 1.20 and 1.25 (total 3H, d, J=6.6 Hz), 0.90 (3H, t, J=6.9 Hz).



Example 54 - process 1

Preparation of N-(tert-butoxycarbonyl)-L-proline 5-methyl-2-oxo-1,3-dioxolene-4-ylmethyl ester (38)

[0099] A solution of 4-hydroxymethyl-5-methyl-2-oxo-1,3-dioxolene (651 mg, 5 mmol) which was synthesized in accordance with the method described in Synthetic Commun., 22, 1277 (1992), tert-butyloxycarbonyl-L-proline (1.07 g, 5 mmol), and 4-dimethylaminopyridine (61 mg, 0.5 mmol) in THF (20 ml) was added DCC (1.14 g, 5.5 mmol) and the resulting mixture was stirred for 16h at room temperature. After the precipitation which appeared was filtered off, the filtrate was concentrated in vacuo. The residue was subjected to silica gel column chromatography (hexane : acetone = 4:1) to give the compound (38) (1.33 g, 81.2%).

NMR($CDCl_3$) : 4.8-5.0 (2H, m), 4.2-4.4 (1H, m), 3.3-3.6 (2H, m), 2.19 and 2.17 (total 3H, s), 1.93 (2H, m), 1.66 (2H, m), 1.45-1.39 (9H, s).

Example 54 - process 2

Preparation of L-proline 5-methyl-2-oxo-1,3-dioxolene-4-ylmethyl ester trifuluoroacetate (39)

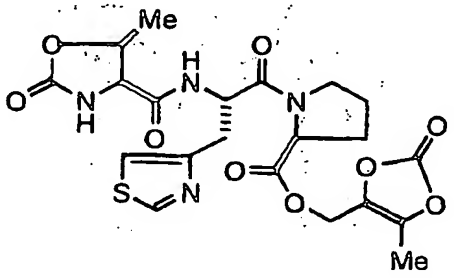
[0100] Trifluoroacetic acid (2.5 ml) was added to the compound (38) (360 mg, 1.1 mmol) under ice-cooling and the resulting mixture was stood for 45 min. To the reaction mixture was added toluene and the mixture was concentrated in vacuo to give 490 mg of the compound (39). This compound was used in the next reaction without purification.

NMR($CDCl_3$): 5.03 (1H, d, J=14.1 Hz), 4.97 (1H, d, J=14.1 Hz), 4.53 (1H, m), 3.52 (2H, m), 2.51 (1H, m), 2.18 (3H, s), 2.18 (3H, s).

Example 54 - process 3

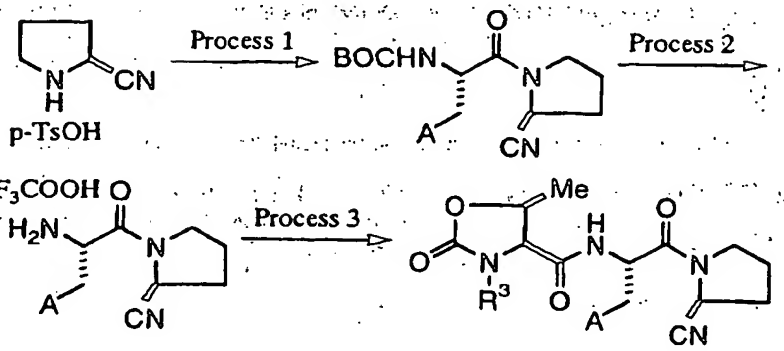
Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-proline 5-methyl-L-proline 5-methyl-2-oxo-1,3-dioxolene-4-ylmethyl ester (I-54)

[0101] In a manner similar to that described in the synthetic method of the compound (34), the compound (29) (299 mg, 1 mmol) was condensed with the compound (39) (130 mg, 0.76 mmol) in the presence of N-hydroxysuccinimide (127 mg, 1.1 mmol), DCC (227 mg, 1.1 mmol), and triethylamine (0.56 ml, 4 mmol) in N, N-dimethylformamide to give 162 mg (30 %) of the compound (I-54). The chemical formula was shown below.



$[\alpha]_D$ = -56.2° (c=0.502, H_2O, 26°C).
NMR(CD_3OD) : 8.97 and 8.96 (total 1H, d, J=2.1 Hz), 7.39 and 7.32 (total 1H, d, J=2.1 Hz), 5.09 (1H, m), 4.96 (2H, s), 4.90 (1H, m), 4.46 (t 1H, m), 4.31(1H, t, J=8.7 Hz), 3.92 (1H, m), 3.61 (1H, m), 3.29 (1H, dd, J=5.4, 14.7 Hz), 3.16 (1H, dd, J=8.4, 14.7 Hz), 2.27 (1H, m), 2.17 (3H, s), 2.00 (3H, m), 1.23 and 1.18 (total 3H, d, J=6.6 Hz).
Elemental analysis ($C_{21}H_{24}N_4O_9S$ 1.1H_2O)

Calcd. :	C,47.74;	H,5.00;	N, 10.60;	S,6.07.
Found :	C,47.78;	H,5.04;	N,10.67;	S,5.97.



Example 55 - process 1

Preparation of N-(tert-butoxycarbonyl)-3-(4-thiazolyl)-L-alanyl-2S-cyanopyrrolidine (40)

[0102] 2S-Cyanopyrrolidine p-toluenesulfonate (440 mg, 1.62 mmol) which was synthesized in accordance with Bioorg. Med. Chem. Lett., 6, 1163 (1996) was condensed with N-(tert-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine (440 mg, 1.62 mmol) in the presence of N-hydroxysuccinimide (190 mg, 1.62 mmol), DCC (370 mg, 1.78 mmol), and triethylamine (0.46 ml, 3.24 mmol) to give 180 mg (31.5 %) of the compound (40).

$[\alpha]_D$ = -37.2° (c=0.503, $CHCl_3$, 26°C)
IR(Nujol)cm^{-1} : 2246, 1697, 1645, 1162.
NMR($CDCl_3$) : 8.79 (1H, d, J=2 Hz), 7.15 (1H, d, J=2 Hz), 5.41 (1H, d, J=8.2 Hz), 4.79 (1H, dd, J=7, 8.2 Hz), 4.72 (1H, dd, J=3.6, 6.9 Hz), 3.62 (1H, m), 3.35 (1H, m), 3.22 (2H, d, J=7 Hz), 1.90-2.3 (4H, m), 1.40(9H, s).
Elemental analysis ($C_{16}H_{22}N_4O_3S$)

Calcd. :	C,54.84;	H,6.33;	N,15.99;	S,9.15.
Found :	C,54.64;	H,6.30;	N,15.80;	S,8.95.

Example 55 - process 2

Preparation of 3-(4-thiazolyl)-L-alanyl-2(S)-cyanopyrrolidine trifluoroacetate (41)

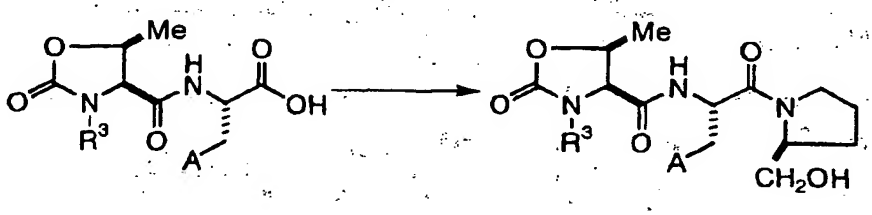
[0103] Trifluoroacetic acid (5 ml) was added to the compound (40) (500 mg, 1.43 mmol) under ice-cooling and the resulting mixture was stirred for 90 min. Toluene was added to the reaction mixture and the mixture was concentrated in vacuo to give 970 mg of the compound (41). This compound was used in the next reaction without purification.

NMR($CDCl_3$) : 8.85 (1H, d, J=2 Hz), 7.31 (1H, d, J=2 Hz), 4.78 (1H, dd, J=4.8, 6.6 Hz), 4.62 (1H, t, J=6.6 Hz), 3.10-3.70 (4H, m), 1.80-2.3 (4H, m).

Example 55 - process 3

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-2(S)-cyanopyrrolidine (I-55)

[0104] In a manner similar to that described in the synthetic method of the compound (34), cis-L-5-methyl-2-oxo-oxazolidine-4-carboxylic acid (210 mg, 1.43 mmol) was condensed with the compound (41) (970 mg, 1.43 mmol) in the presence of N-hydroxysuccinimide (160 mg, 1.43 mmol), DCC (320 mg, 1.57 mmol), and triethylamine (0.6 ml, 4.29 mmol) in N, N-dimethylformamide to 330 mg of compound (I-55). The result was shown in Table 23.



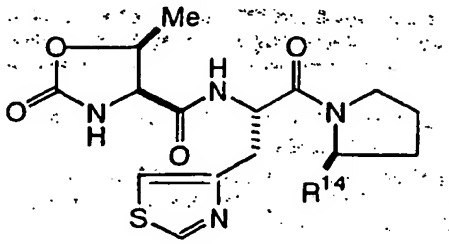
Example 56

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-L-prolinol (I-56)

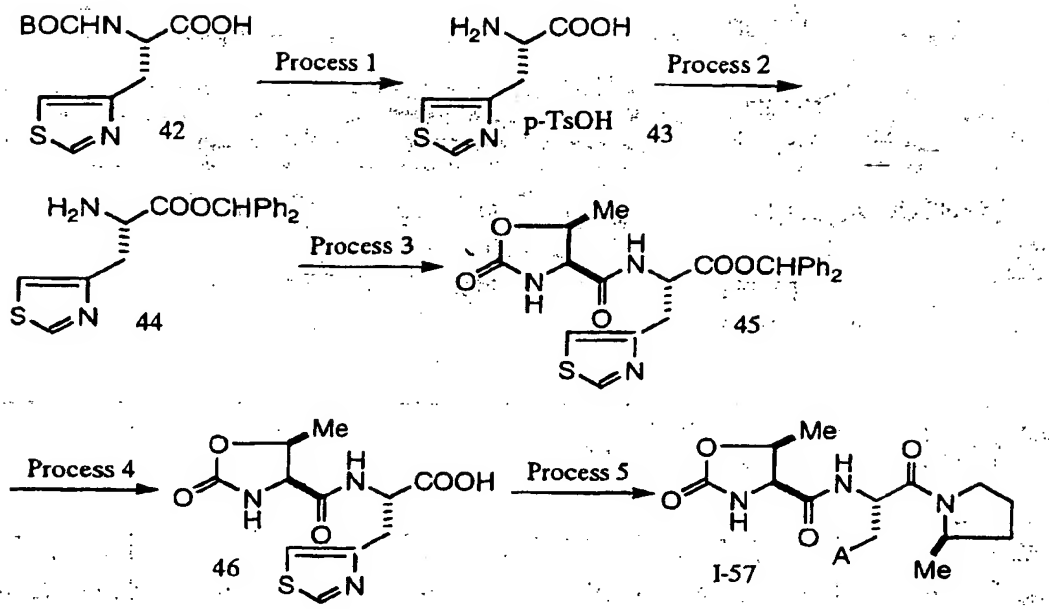
[0105] In a manner similar to that described in the synthetic method of the compound of (34), the compound of (29) (299 mg, 1 mmol) was condensed with L-prolinol (101 mg, 1 mmol) in the presence of N-hydroxysuccinimide (127 mg,

1.1 mmol), DCC (227 mg, 1.1 mmol), and triethylamine (0.15 ml, 1.1 mmol) in N, N-dimethylformamide to give 162 mg of the compound (I-56). The result was shown in Table 23.

Table 23



Example No.	Compound No.	R^{14}	$[\alpha]_D$	NMR
55-3	I-55	-CN	-35.0° (c=1.007, MeOH, 25°C)	(CD_3OD): 8.98 (1H, d, J=2 Hz), 7.35 (1H, d, J=2.1 Hz), 4.90-5.00 (2H, m), 4.70 (1H, dd, J=8, 3.6 Hz), 4.34 (1H, d, J=8.4 Hz), 3.77 (1H, m), 3.43 (1H, m), 3.30 (1H, m), 3.24 (1H, dd, J=7.2, 14.1 Hz), 2.10 (4H, m), 1.23 (3H, d, J=6.3 Hz).
56	I-56	$-CH_2OH$	-10.7° (c=0.506, H_2O, 26°C)	(CD_3OD): 8.98 and 8.95 (total 1H, d, J=2.1 Hz), 7.36 and 7.35 (1H, d, J=2.1 Hz), 5.21 and 5.06 (1H, t, J=7.5 Hz), 4.91 (1H, m), 4.37 and 4.35 (total 1H, d, J=8.7 Hz), 4.06 (1H, m), 3.7-3.9 (1H, m), 3.51 (1H, dd, J=3.9, 10.8 Hz), 3.43 (1H, dd, J=6.3, 10.8 Hz), 3.40 (1H, m), 3.25 (2H, m), 1.6-2.0 (4H, m), 1.25 and 1.22 (total 3H, d, J=6.3 Hz).



Example 57 - process 1

Preparation of 3-(4-thiazolyl)-L-alanine p-toluenesulfonate (43)

[0106] Trifluoroacetic acid (80 ml) was added to N-(tert-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine (42, 21.79 g, 80 mmol) which was synthesized in accordance with the method described in the literature (Synth. Commun., 20, 3507 (1990)) and the resulting mixture was stirred for 2h under ice-cooling. Subsequently, to the mixture was added p-toluenesulfonic acid hydrate (15.22 g, 80 mmol) and the resulting mixture was stirred for 30 min. at room temperature. The reaction mixture was concentrated in vacuo. To the residue was added water and methanol, and excess trifluoroacetic acid was removed by concentrating in vacuo. To the residue was added diethyl ether and the precipitation which appeared was filtered off to give 29.8 g (quantitative) of the compound (43).

NMR(CD_3OD) : 9.01 (1H, d, J=1.8 Hz), 7.70 (2H, m), 7.46 (1H, d, J=1.8 Hz), 7.23 (2H, m), 4.38 (1H, dd, J=4.8 and 7.6 Hz), 3.45 (2H, m), 2.37 (3H, s).

Example 57 - process 2

Preparation of 3-(4-thiazolyl)-L-alanine diphenylmethylester p-toluenesulfonate (44)

[0107] To a solution of 38.85 g of the compound (43) (112.8 mmol) in ethanol (200 ml) - THF (600 ml) was added diphenyldiazomethane (39 g, 201 mmol) little by little over 30 min. at room temperature with stirring. After the reaction mixture was stirred for 1h at room temperature, to the mixture was added diphenyldiazomethane (10 g, 51.5 mmol) and the resulting mixture was stirred for 1h. To the reaction mixture was added acetic acid (0.1 ml) for quenching the excess reagent and the mixture was concentrated in vacuo. The residue (92 g) was crystallized by adding ether (1 L) to give 49.05 g (96.1 %) of the compound (44).

mp: 139 - 140°C
$[\alpha]_D$ = -34.7° (c=1.006, $CHCl_3$, 23°C)
IR(KBr)cm^{-1}: 1753, 1602, 1512, 1496, 1260, 1224, 1171, 1124, 1036, 1012.

NMR(CD_3OD) : 8.92 (1H, d, J=2 Hz), 7.70 (2H, m), 7.2-7.4 (13H, m), 6.91 (1H, s), 4.62 (1H, t, J=5.8 Hz), 3.47 (2H, d, J=5.8 Hz), 2.36 (3H, s).

Elemental analysis ($C_{26}H_{26}N_2O_5S_2$)

Calcd. :	C,61.16;	H,5.13;	N,5.49;	S,12.56.
Found :	C,61.14;	H,5.32;	N,5.41;	S,12.46.

Example 57 - process 3

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanine diphenylmethyl ester (45)

[0108] A solution of 13.95 g (96.14 mmol) of cis-L-5-methyl-2-oxo-oxazolidine-4-carboxylic acid, 49.09 g (96.14 mmol) of the compound (44), 2.6 g (19.23 mmol) of N-hydroxybenzotriazole, and 14.1 ml (101 mmol) of triethylamine in THF (1 L) was added DCC (20.83 g, 101 mmol) under ice-cooling. After the mixture was stirred for 10 min. at the same temperature, the ice-cooling bath was removed and the reaction mixture was stirred for 20h at room temperature. After the precipitation which appeared was filtered off, the filtrate was concentrated in vacuo to give oily residue (82.7 g). The reside was dissolved in ethyl acetate (700 ml) with heating and the precipitation which appeared was filtered off. The filtrate was washed with sodium carbonate aq. and water. After methanol (20 ml) was added to the organic layer, the organic layer was dried over magnesium sulfate and concentrated in vacuo. The precipitated crystal was filtered off and washed with ethyl acetate-ether (2:3) to give 35.69 g (79.8 %) of the compound (45). After the mother liquor was concentrated in vacuo, the residue was crystallized from ethyl acetate - ether to give 2.62 g (5.9 %) of the compound (45).

mp: 176-177°C

$[\alpha]_D$ = -39.2° (c=1.007, $CHCl_3$, 24°C)

IR(KBr)cm^{-1} : 1739, 1681, 1508, 1453, 1386, 1237, 1193, 1089.

NMR($CDCl_3$) : 8.71(1H, d, J=1.8 Hz), 8.18 (1H, d, J=7.8 Hz), 7.2-7.4 (10H, m), 6.82 (1H, s), 6.66 (1H, d, J=1.8 Hz), 5.79 (1H, s), 5.12 (1H, m), 4.94 (1H, m), 4.35 (1H, dd, J=1.8 and 9.0 Hz), 3.40 (1H, dd, J=5.7 and 15 Hz), 3.29 (1H, dd, J=4.5 and 15 Hz), 1.27 (3H, d, J=6.3 Hz).

Elemental analysis ($C_{24}N_{23}N_3O_5S$)

Calcd. :	C,61.92;	H,4.98;	N,9.03;	S,6.89.
Found :	C,61.95;	H,5.01;	N,8.94;	S,6.62.

Example 57 - process 4

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanine(46)

[0109] Anisole (240 ml) and trifluoroacetic acid (120 ml) was added to 41.24 g (88.59 mmol) of the compound (45) under ice-cooling and the resulting mixture was stirred for 15 min. After the cooling bath was removed, the mixture was stirred for 2.5h at room temperature. The reaction mixture was concentrated in vacuo to give oily residue. To the residue was added ether (500 ml) and the precipitation which appeared was filtered off as powder. The powder was dissolved in water (50 ml) - methanol (300 ml) with heating and the precipitation which appeared was filtered off. The filtrate was concentrated in vacuo. To the residue was added the seed crystal and methanol and the resulting mixture was stood for 3 days at room temperature. The precipitated crystal was filtered off to give 14.89 g (56.1 %) of the compound (46). The mother liquor was concentrated in vacuo and the residue was crystallized from methanol - ether to give 10.3 g (38 %) of the compound (46).

mp : 214-215°C

IR(KBr)cm^{-1} : 1753, 1707, 1655, 1548, 1529, 1409, 1343, 1264, 1236, 1102, 1092.

NMR(DMSO-d6) : 9.02 (1H, d, J=1.8 Hz), 8.46 (1H, d, J=7.8 Hz), 7.74 (1H, s), 7.38 (1H, d, J=1.8 Hz), 4.77 (1H, dq, J=6.6 and 8.7 Hz), 4.66 (1H, m), 4.21 (1H, d, J=8.7 Hz), 3.24 (1H, dd, J=5.1 and 15 Hz), 3.13 (1H, dd, J=8.4 and 15 Hz), 1.13 (3H, d, J=6.6 Hz).

Elemental analysis ($C_{11}H_{13}N_3O_5S$)

Calcd. :	C,44.14;	H,4.38;	N,14.04;	S,10.71.
Found :	C,43.94;	H,4.478;	N,14.09;	S,10.58.

Example 57 - process 5

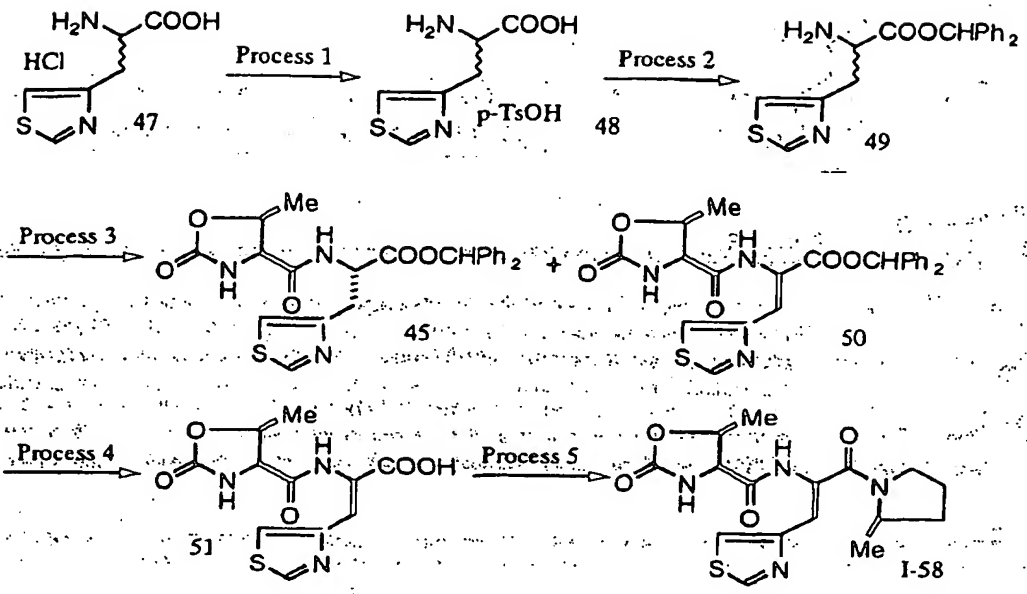
Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanyl-2(R)-methylpyrrolidine (I-57)

[0110] (Method A) To a suspension of 12.1 (40.48 mM) of the compound (46) and N-hydroxysuccinimide (4.66 g, 40.48 mM) in THF (242 ml) was added DCC (8.35 g, 40.48 mM) under ice-cooling and the resulting mixture was stirred for 30 min. The cooling bath was removed and the reaction mixture was stirred for 2h at room temperature additionally. To a suspension of (R)-(+)-2-methylpyrrolidine hydrochloride (5.42 g) which was synthesized in accordance with the method described in the literature (Tetrahedron, 27, 2599 (1971)) and triethylamine (8.46 ml, 60.72 mM) in THF (121 ml) was added the solution containing N-hydroxysuccinimide ester of the compound (46) at room temperature. The reaction mixture was stirred for additional 15h. After the precipitation which appeared was filtered off, the filtrate was concentrated in vacuo. The residue (24.6 g) was subjected to gel filtration column chromatography (MCI Gel CHP-20P, 600 ml). The fractions eluting with 40% aqueous methanol were collected to give 8.87 g of the crude compound (I-57). After the crude compound was subjected to silica gel column chromatography (chloroform - methanol), the purified compound was freeze-dried to give 5.37 g (35.7 %) of the compound (I-57).

mp : 192-194°C
$[\alpha]_D$ = -1.9° (c=1.005, H_2O, 25°C)
IR(KBr)cm^{-1} : 1755, 1675, 1625, 1541, 1516, 1448, 1232, 1097.
NMR(CD_3OD) : 8.97 (1H, t, J=2.1 Hz), 7.34 (1H, t, J=2.1 Hz), 5.19 and 5.04 (total 1H, each t, J=7.5 Hz), 4.92 (1H, dq, J=6.6 and 8.7 Hz), 4.36 and 4.35 (1H, d, J=8.7 Hz), 4.07 and 3.92 (total 1H, each m), 3.78 (1H, m), 3.42 (1H, m), 3.22 (2H, m), 1.5-2.0 (4H, m), 1.28 and 1.22 (total 3H, each d, J=6.6 Hz), 1.21 and 1.02 (total 3H, each d, J=6.6 Hz),
Elemental analysis ($C_{16}H_{22}N_4O_4S\ H_2O$)

Calcd. :	C,49.99;	H,6.29;	N,14.57;	S,8.34.
Found :	C,49.99;	H,6.29;	N,14.79;	S,8.36.

[0111] (Method B) To a solution of 10 g (33.41 mol) of the compound (46) and N-hydroxysuccinimide (4.04 g, 35.08 mM) in DMF (45 ml) - THF (360 ml) was added DCC (7.24 g, 35.08 mM) under ice-cooling and the resulting mixture was stirred for 4h. To this reaction mixture was added a solution of (R)-(+)-2-methylpyrrolidine p-toluenesulfonate (8.6 g) which was synthesized in accordance with the method described in the literature (Helv. Chim. Acta, 34, 2202 (1951)) and triethylamine (9.32 ml, 66.82 mmol) in THF (11 ml) under ice-cooling. After the mixture was stirred for 4h at the same temperature, the cooling bath was removed and the mixture was stirred for 48 h. After the precipitation which appeared was filtered off, the filtrate was concentrated in vacuo. The residue (38 g) was dissolved in water (220 ml) and the precipitation which appeared was filtered off. The filtrate was subjected to gel column chromatography (MCI Gel CHP-20P, 600 ml). The fractions eluting with 40 % aqueous methanol were collected and crystallized from water to give 6.94 g (56.7%) of the same compound (I-56) that the compound had been synthesized in Method A.



Example 58 - process 1

Preparation of 3-(4-thiazolyl)-DL-alanine p-toluenesulfonate (48)

[0112] 17.16 g (70 mmol) of 3-(4-Thiazolyl)-DL-alanine hydrochloride (47) was dissolved in purified water (100 ml) and the resulting mixture was adsorbed on ion exchange resin Amberlite IR-120 B (Organo inc.) (120 ml, Type-H) column. The column was washed with water and the fractions eluting with ammonia water to yield the free base of the compound (47) (11.04 g).

NMR(D_2O): 8.98 (1H, d, J=1.8 Hz), 7.42 (1H, d, J=1.8 Hz), 4.08 (1H, dd, J=4.8 and 7.8 Hz), 3.45 (1H, dd, J=4.8 and 15.3 Hz), 3.33 (1H, dd, J=7.8 and 15.3 Hz).

[0113] After the free base (11.04 g) was suspended in water (50 ml), to the suspension was added a solution of p-toluenesulfonic acid hydrate (12.19 g) in water (50 ml). The mixture was concentrated in vacuo to give syrupy residue (24.43 g). To the residue was added methanol (10 ml) and ether (300 ml) and the precipitated crystal was filtered off to give 21.84 g (98.9%) of the compound (48).

NMR(CD_3OD) : 9.00 (1H, d, J=2.1 Hz). 7.71 (2H, m), 7.46 (1H, J=2.1 Hz), 7.23 (2H, m), 4.37 (1H, dd, J=4.5 and 7.5 Hz). 3.50 (1H, dd, J=4.5 and 15.9 Hz). 3.38 (1H, dd, J=7.5 and 15.9 Hz), 2.36 (3H, s).

Example 58 - process 2

Preparation of 3-(4-thiazolyl)-DL-alanine diphenylmethyl ester p-toluenesulfonate (49)

[0114] After 21.84 g (123.6 mmol) of the compound (48) was dissolved in ethanol (200 ml) and THF (100 ml) with heating, to the solution was added diphenyldiazomethane (24 g, 123.6 mmol) under ice-cooling over 35 min. little by little. The cooling bath was removed and the mixture was stirred for 1h at room temperature. To the reaction mixture was added acetic acid (0.1 ml) for quenching the excess reagent and the mixture was concentrated in vacuo. The residue was crystallized from ether and ethanol to yield 31.63 g (97.7%) of the compound (49).

mp : 148-149°C
IR(KBr)cm^{-1} : 1755, 1607, 1516, 1493, 1216, 1202, 1181, 1125, 1088, 1066, 1036, 1011.
NMR(CD_3OD): 8.92 (1H, d, J=2.1 Hz), 7.70 (2H, m), 7.2-7.4 (13H, m), 6.91 (1H, s), 4.62 (1H, t, J=6 Hz), 3.47 (2H, d, J=6 Hz), 2.36 (3H, s).
Elemental analysis ($C_{26}N_{26}N_2O_5S_2$)

Calcd. :	C,61.16;	H,5.13;	N,5.49;	S,12.56.
Found :	C,60.98;	H,5.06;	N,5.45;	S,12.40.

Example 58 - process 3

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-L-alanine diphenylmethyl ester (45) and cis-L-5-methyl-2-oxo-oxazolidine-4-carbonyl-3-(4-thiazolyl)-D-alanine diphenylmethyl ester (50).

[0115] In a manner similar to that described in the above process 3, cis-L-5-methyl-2-oxo-oxazoline-4-carboxylic acid (8.14 g, 56.07 mmol) was condensed with 28.63 g (56.07 mmol) of the compound (49) using DCC (12.15 g, 58.87 mmol) in the presence of N-hydroxybenzotriazole (1.52 g, 11.21 mmol) and triethylamine (8.21 ml, 58.87 mmol) in the mixed solvents of DMF (100 ml) - THF (580 ml). After the precipitation which appeared was filtered off, the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate (400 ml) with heating and the precipitation which appeared was filtered off. The filtrate was washed with sodium carbonate aq. and water. After the ethyl acetate layer was stood overnight and the precipitated crystal was filtered off, the crystal was recrystallized from ethyl acetate - methanol to give 4.6 g (17.6%) of the compound (50).

mp : 203-204°C
$[\alpha]_D$ = +27.5° (c=1, DMF, 22°C)
IR(KBr)cm^{-1}: 1754, 1738, 1664, 1523, 1381, 1228, 1207, 1171, 1100.
NMR(DMSO-d6) : 9.02 (1H, d, J=1.8 Hz), 8.67 (1H, d, J=7.8 Hz), 7.82 (1H, s), 7.2-7.4 (1H, m), 6.79 (1H, s), 5.00(1H, m), 4.68 (1H, m), 4.19 (1H, d, J=8.4 Hz), 3.2-3.4 (1H, m), 3.16 (1H, dd, J=9.3 and 14.4 Hz), 0.81(3H, d, J=6.3 Hz).
Elemental analysis ($C_{24}H_{23}N_3O_5S$)

Calcd. :	C,61.92;	H,4.98;	N,9.03;	S,6.89.
Found :	C,61.60;	H,5.04;	N,9.22;	S,6.96.

[0116] The mother liquor which was obtained by collecting the crystals was concentrated in vacuo, the precipitated crystal was filtered off to give 17.26 g (76.1 %) of the mixture of the compounds (50) and (45). The mixture was crystallized from methanol - ethyl acetate to yield 3.92 g (15 %) of the compound (50). After the mother liquor was concentrated in vacuo, the residue was crystallized from acetone - ether to give 6.21 g (23.7 %) of the same compound (45) that the compound had been synthesized in Example 57 - process 3.

Example 58 - process 4

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3-(4-thiazolyl)-D-alanine (51)

[0117] In a manner similar to that described in the method of Example 57 - process 4, 4.1 g (8.81 mmol) of the compound (50) was de-diphenylmethylesterificated by treating with trifluoroacetic acid - anisole to give 206 g (78.3 %) of the compound (51).

mp : 214°C
$[\alpha]_D$= + 6.9° (c=0.5, DMF, 22°C)
IR(KBr)cm^{-1} : 1753, 1708, 1657, 1560, 1413, 1343, 1280, 1241, 1175, 1095.
NMR(DMSO-d6) 9.02 (1H, d, J=2.1 Hz), 8.46 (1H, d, J=8.1 Hz), 7.78 (1H, s), 7.40 (1H, d, J=8.4 Hz), 4.6-4.8 (2H,

m), 4.18 (1H, d, J=8.4 Hz), 3.25 (1H, dd, J=4.2 and 15 Hz), 3.10 (1H, dd, J=9.9 Hz and 15 Hz), 0.80 (3H, d, J=6.6 Hz).

Elemental analysis ($C_{11}H_{13}N_3O_5S$)

Calcd. :	C,44.14;	H,4.38;	N,14.04;	S,10.71.
Found :	C,44.08;	H,4.39;	N,14.04;	S,10.71.

Example 58 - process 5

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-yl-carbonyl-3(4-thiazolyl)-D-alanyl-2(R)-methylpyrrolidine (I-58)

[0118] In a manner similar to that described in the method of Example 57 - process 5, the compound (51) was condensed with 2(R)-methylpyrrolidine p-toluenesulfonate in the presence of N-hydroxysuccinimide, DCC, and triethylamine in DMF - THF to give the compound (I-58).

mp 170-172°C

$[\alpha]_D$ = - 16.2° (c=1.014, MeOH, 25°C)

IR(KBr)cm^{-1} : 1749, 1661, 1637, 1538, 1441, 1381, 1264.

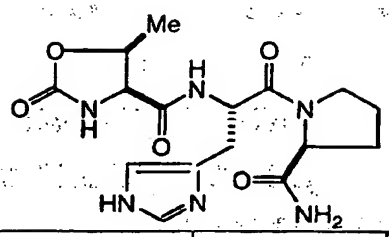
NMR(CD_3OD) : 8.97 (1H, t, J=2.1 Hz), 7.34 (1H, t, J=2.1 Hz), 5.19 and 5.04 (total 1H, each t, J=7.5 Hz), 4.92 (1H, dq, J=6.6 and 8.7 Hz), 4.36 and 4.35 (1H, d, J=8.7 Hz), 4.07 and 3.92 (total 1H, each m), 3.78 (1H, m), 3.42 (1H, m), 3.22 (2H, m), 1.5-2.0 (4H, m), 1.28 and 1.22 (total 3H, each d, J=6.6 Hz), 1.21 and 1.02 (total 3H, each d, J=6.6 Hz).

Elemental analysis ($C_{16}H_{22}N_4O_4S\ H_2O$)

Calcd. :	C,49.99;	H,6.29;	N,14.57;	S,8.34.
Found :	C,52.40;	H,5.98;	N,15.19;	S,8.77.

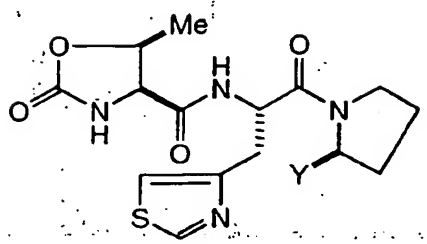
[0119] In a manner similar to that described in the method of the above, the compounds below may be able to be synthesized.

Table 24



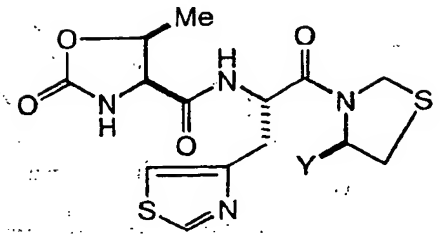
Example No.	Y	Example No.	Y
59	Et	83	-CONHMe
60	n-Pr	84	-CON(Me)$_2$
61	i-Pr	85	-CON(Me)(Et)
62	c-Pr	86	-CON(Et)$_2$
63	n-Bu	87	-CH$_2$-(c-Pr)
64	sec-Bu	88	-CH$_2$-(c-Bu)
65	i-Bu	89	-CH$_2$-(c-Pen)
66	t-Bu	90	-CH$_2$-(c-Hex)
67	c-Bu	91	-CH$_2$CN
68	n-Pen	92	-CH$_2$CHO
69	c-Pen	93	-CH$_2$COOH
70	n-Hex	94	-CH$_2$COOMe
71	c-Hex	95	-CH$_2$COOEt
72	-COOMe	96	-CH$_2$COO(n-Pr)
73	-COOEt	97	-CH$_2$COO(i-Pr)
74	-COO(n-Pr)	98	-CH$_2$COO(c-Pr)
75	-COO(c-Pr)	99	-CH$_2$CF$_3$
76	-COO(n-Bu)	100	-CH$_2$CONH$_2$
77	-COO(c-Bu)	101	-CH$_2$C(O)CH$_3$
78	-COO(c-Pen)	102	-CH$_2$C(O)Et
79	-COO(c-Hex)	103	-CH$_2$C(O)Pr
80	-COO(n-Dec)	104	-CH$_2$Ph
81	-COO(4-Me-Ph)	105	-CH$_2$(4-Me-Ph)
82	-COOPh	106	-CH$_2$SH

Table 25



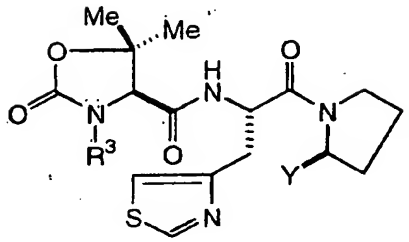
Example No.	Y	Example No.	Y
107	-CH_2SMe	131	-$CH_2PO(OH)_2$
108	-CH_2NO_2	132	-$CH_2PO(OH)$
109	-CH_2NH_2	133	-$CH_2PO(OMe)_2$
110	-CH_2NHMe	134	-CH_2CH_2OH
111	-$CH_2N(Me)_2$	135	-CH_2CH_2OMe
112	-$CH_2N(Me)(Et)$	136	-CH_2CH_2CN
113	-$CH_2OC(O)CH_3$	137	-CH_2CH_2CHO
114	-$CH_2OC(O)Et$	138	-CH_2CH_2COOH
115	-$CH_2OC(O)Ph$	139	-CH_2CH_2COOMe
116	-CH_2OMe	140	-$CH_2CH_2CONH_2$
117	-CH_2OEt	141	-$CH_2CH_2NO_2$
118	-$CH_2O(n\text{-}Pr)$	142	-$(CH_2)_3CN$
119	-$CH_2O(c\text{-}Pr)$	143	-$(CH_2)_3CHO$
120	-$CH_2O(n\text{-}Bu)$	144	-$(CH_2)_3COOH$
121	-$CH_2O(t\text{-}Bu)$	145	-$(CH_2)_3COOMe$
122	-$CH_2O(c\text{-}Pen)$	146	-$(CH_2)_3CONH_2$
123	-$CH_2O(c\text{-}Hex)$	147	-$(CH_2)_3NO_2$
124	-CH_2OPh	148	-CH_2-(1-Pyrrolidinyl)
125	-CH_2SO_3H	149	-CO-(1-Piperidyl)
126	-CH_2SO_3Me	150	-CO-(1-Piperazinyl)
127	-CH_2SO_2Me	151	-CO-(1-Pyrrolyl)
128	-CH_2SO_2Ph	152	-CO-(1-Imidazolizinyl)
129	-CH_2SOMe	153	-CO-(1-Indolyl)
130	-CH_2SOEt	154	-CO-(1-Imidazolyl)

Table 26



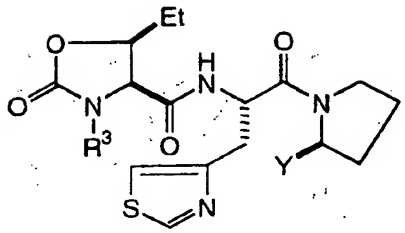
Example No.	Y	Example No.	Y
155	Me	179	-CH_2CN
156	Et	180	-CH_2CHO
157	n-Pr	181	-CH_2COOH
158	i-Pr	182	-CH_2COOMe
159	c-Pr	183	-CH_2COOEt
160	n-Bu	184	-CH_2COO(n-Pr)
161	i-Bu	185	-CH_2COO(i-Pr)
162	sec-Bu	186	-CH_2COO(c-Pr)
163	c-Bu	187	-CH_2COOPh
164	n-Pen	188	-CH_2CONH_2
165	c-Pen	189	-$CH_2C(O)CH_3$
166	n-Hex	190	-$CH_2C(O)Et$
167	c-Hex	191	-$CH_2C(O)Pr$
168	-COOMe	192	-CH_2SH
169	-COOEt	193	-CH_2SMe
170	-COO(n-Pr)	194	-CH_2NO_2
171	-COO(c-Pr)	195	-CH_2NH_2
172	-COO(n-Bu)	196	-CH_2NHMe
173	-COO(c-Bu)	197	-$CH_2N(Me)_2$
174	-COO(c-Pen)	198	-$CH_2OC(O)CH_3$
175	-COO(c-Hex)	199	-$CH_2OC(O)Et$
176	-CONHMe	200	-$CH_2OC(O)Ph$
177	-$CON(Me)_2$	201	-CH_2-(1-Pyrrolidinyl)
178	-CON(Me)(Et)	202	-CO-(1-Piperidyl)

Table 27



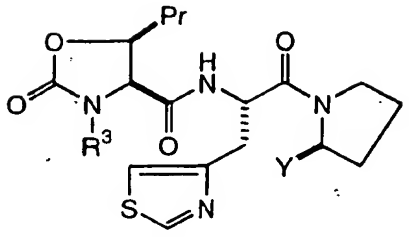
Example No.	R^3	Y	Example No.	R^3	Y
203	H	Me	227	Me	Me
204	H	Et	228	Me	Et
205	H	n-Pr	229	Me	n-Pr
206	H	i-Pr	230	Me	i-Pr
207	H	c-Pr	231	Me	c-Pr
208	H	n-Bu	232	Me	n-Bu
209	H	i-Bu	233	Me	i-Bu
210	H	sec-Bu	234	Me	sec-Bu
211	H	t-Bu	235	Me	t-Bu
212	H	-COOH	236	Me	-COOH
213	H	-COOMe	237	Me	-COOMe
214	H	$-CONH_2$	238	Me	$-CONH_2$
215	H	-CONHMe	239	Me	-CONHMe
216	H	-CN	240	Me	-CN
217	H	$-CH_2OH$	241	Me	$-CH_2OH$
218	H	$-CH_2OMe$	242	Me	$-CH_2OMe$
219	H	$-CH_2COOH$	243	Me	$-CH_2COOH$
220	H	$-CH_2COOMe$	244	Me	$-CH_2COOMe$
221	H	$-CH_2COPh$	245	Me	$-CH_2COPh$
222	H	$-CH_2CONH_2$	246	Me	$-CH_2CONH_2$
223	H	$-CH_2CN$	247	Me	$-CH_2CN$
224	H	$-CH_2CHO$	248	Me	$-CH_2CHO$
225	H	$-CH_2CF_3$	249	Me	$-CH_2CF_3$
226	H	$-CH_2SH$	250	Me	$-CH_2SH$

Table 28



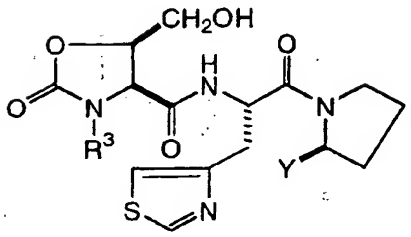
Example No.	R^3	Y	Example No.	R^3	Y
251	H	Me	275	Me	Me
252	H	Et	276	Me	Et
253	H	n-Pr	277	Me	n-Pr
254	H	i-Pr	278	Me	i-Pr
255	H	c-Pr	279	Me	c-Pr
256	H	n-Bu	280	Me	n-Bu
257	H	i-Bu	281	Me	i-Bu
258	H	sec-Bu	282	Me	sec-Bu
259	H	t-Bu	283	Me	t-Bu
260	H	-COOH	284	Me	-COOH
261	H	-COOMe	285	Me	-COOMe
262	H	$-CONH_2$	286	Me	$-CONH_2$
263	H	-CONHMe	287	Me	-CONHMe
264	H	-CN	288	Me	-CN
265	H	$-CH_2OH$	289	Me	$-CH_2OH$
266	H	$-CH_2OMe$	290	Me	$-CH_2OMe$
267	H	$-CH_2COOH$	291	Me	$-CH_2COOH$
268	H	$-CH_2COOMe$	292	Me	$-CH_2COOMe$
269	H	$-CH_2COPh$	293	Me	$-CH_2COPh$
270	H	$-CH_2CONH_2$	294	Me	$-CH_2CONH_2$
271	H	$-CH_2CN$	295	Me	$-CH_2CN$
272	H	$-CH_2CHO$	296	Me	$-CH_2CHO$
273	H	$-CH_2CF_3$	297	Me	$-CH_2CF_3$
274	H	$-CH_2SH$	298	Me	$-CH_2SH$

Table 29



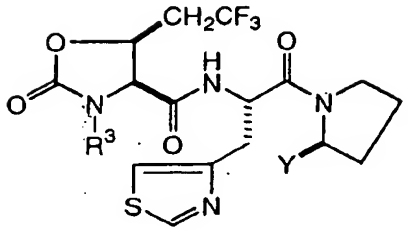
Example No.	R^3	Y	Example No.	R^3	Y
299	H	Me	323	Me	Me
300	H	Et	324	Me	Et
301	H	n-Pr	325	Me	n-Pr
302	H	i-Pr	326	Me	i-Pr
303	H	c-Pr	327	Me	c-Pr
304	H	n-Bu	328	Me	n-Bu
305	H	i-Bu	329	Me	i-Bu
306	H	sec-Bu	330	Me	sec-Bu
307	H	t-Bu	331	Me	t-Bu
308	H	-COOH	332	Me	-COOH
309	H	-COOMe	333	Me	-COOMe
310	H	$-CONH_2$	334	Me	$-CONH_2$
311	H	-CONHMe	335	Me	-CONHMe
312	H	-CN	336	Me	-CN
313	H	$-CH_2OH$	337	Me	$-CH_2OH$
314	H	$-CH_2OMe$	338	Me	$-CH_2OMe$
315	H	$-CH_2COOH$	339	Me	$-CH_2COOH$
316	H	$-CH_2COOMe$	340	Me	$-CH_2COOMe$
317	H	$-CH_2COPh$	341	Me	$-CH_2COPh$
318	H	$-CH_2CONH_2$	342	Me	$-CH_2CONH_2$
319	H	$-CH_2CN$	343	Me	$-CH_2CN$
320	H	$-CH_2CHO$	345	Me	$-CH_2CHO$
321	H	$-CH_2CF_3$	346	Me	$-CH_2CF_3$
322	H	$-CH_2SH$	347	Me	$-CH_2SH$

Table 30



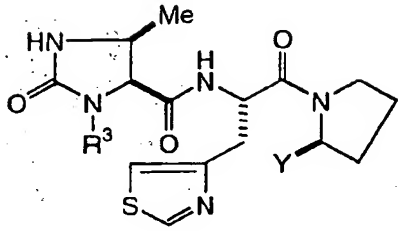
Example No.	R^3	Y	Example No.	R^3	Y
348	H	Me	372	Me	Me
349	H	Et	373	Me	Et
350	H	n-Pr	374	Me	n-Pr
351	H	i-Pr	375	Me	i-Pr
352	H	c-Pr	376	Me	c-Pr
353	H	n-Bu	377	Me	n-Bu
354	H	i-Bu	378	Me	i-Bu
355	H	sec-Bu	379	Me	sec-Bu
356	H	t-Bu	380	Me	t-Bu
357	H	-COOH	381	Me	-COOH
358	H	-COOMe	382	Me	-COOMe
359	H	$-CONH_2$	383	Me	$-CONH_2$
360	H	-CONHMe	384	Me	-CONHMe
361	H	-CN	385	Me	-CN
362	H	$-CH_2OH$	386	Me	$-CH_2OH$
363	H	$-CH_2OMe$	387	Me	$-CH_2OMe$
364	H	$-CH_2COOH$	388	Me	$-CH_2COOH$
365	H	$-CH_2COOMe$	389	Me	$-CH_2COOMe$
366	H	$-CH_2COPh$	390	Me	$-CH_2COPh$
367	H	$-CH_2CONH_2$	391	Me	$-CH_2CONH_2$
368	H	$-CH_2CN$	392	Me	$-CH_2CN$
369	H	$-CH_2CHO$	393	Me	$-CH_2CHO$
370	H	$-CH_2CF_3$	394	Me	$-CH_2CF_3$
371	H	$-CH_2SH$	395	Me	$-CH_2SH$

Table 31



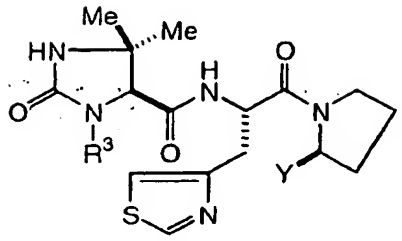
Example No.	R^3	Y	Example No.	R^3	Y
396	H	Me	420	Me	Me
397	H	Et	421	Me	Et
398	H	n-Pr	422	Me	n-Pr
399	H	i-Pr	423	Me	i-Pr
400	H	c-Pr	424	Me	c-Pr
401	H	n-Bu	425	Me	n-Bu
402	H	i-Bu	426	Me	i-Bu
403	H	sec-Bu	427	Me	sec-Bu
404	H	t-Bu	428	Me	t-Bu
405	H	-COOH	429	Me	-COOH
406	H	-COOMe	430	Me	-COOMe
407	H	$-CONH_2$	431	Me	$-CONH_2$
408	H	-CONHMe	432	Me	-CONHMe
409	H	-CN	433	Me	-CN
410	H	$-CH_2OH$	434	Me	$-CH_2OH$
411	H	$-CH_2OMe$	435	Me	$-CH_2OMe$
412	H	$-CH_2COOH$	436	Me	$-CH_2COOH$
413	H	$-CH_2COOMe$	437	Me	$-CH_2COOMe$
414	H	$-CH_2COPh$	438	Me	$-CH_2COPh$
415	H	$-CH_2CONH_2$	439	Me	$-CH_2CONH_2$
416	H	$-CH_2CN$	440	Me	$-CH_2CN$
417	H	$-CH_2CHO$	441	Me	$-CH_2CHO$
418	H	$-CH_2CF_3$	442	Me	$-CH_2CF_3$
419	H	$-CH_2SH$	443	Me	$-CH_2SH$

Table 32



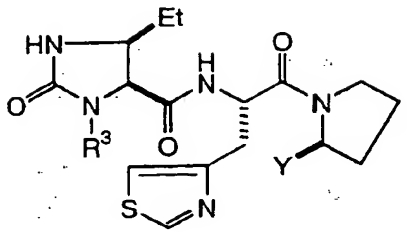
Example No.	R^3	Y	Example No.	R^3	Y
444	H	Me	468	Me	Me
445	H	Et	469	Me	Et
446	H	n-Pr	470	Me	n-Pr
447	H	i-Pr	471	Me	i-Pr
448	H	c-Pr	472	Me	c-Pr
449	H	n-Bu	473	Me	n-Bu
450	H	i-Bu	474	Me	i-Bu
451	H	sec-Bu	475	Me	sec-Bu
452	H	t-Bu	476	Me	t-Bu
453	H	-COOH	477	Me	-COOH
454	H	-COOMe	478	Me	-COOMe
455	H	$-CONH_2$	479	Me	$-CONH_2$
456	H	-CONHMe	480	Me	-CONHMe
457	H	-CN	481	Me	-CN
458	H	$-CH_2OH$	482	Me	$-CH_2OH$
459	H	$-CH_2OMe$	483	Me	$-CH_2OMe$
460	H	$-CH_2COOH$	484	Me	$-CH_2COOH$
461	H	$-CH_2COOMe$	485	Me	$-CH_2COOMe$
462	H	$-CH_2COPh$	486	Me	$-CH_2COPh$
463	H	$-CH_2CONH_2$	487	Me	$-CH_2CONH_2$
464	H	$-CH_2CN$	488	Me	$-CH_2CN$
465	H	$-CH_2CHO$	489	Me	$-CH_2CHO$
466	H	$-CH_2CF_3$	490	Me	$-CH_2CF_3$
467	H	$-CH_2SH$	491	Me	$-CH_2SH$

Table 33



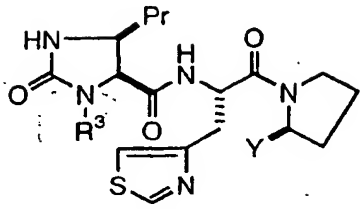
Example No.	R^3	Y	Example No.	R^3	Y
492	H	Me	516	Me	Me
493	H	Et	517	Me	Et
494	H	n-Pr	518	Me	n-Pr
495	H	i-Pr	519	Me	i-Pr
496	H	c-Pr	520	Me	c-Pr
497	H	n-Bu	521	Me	n-Bu
498	H	i-Bu	522	Me	i-Bu
499	H	sec-Bu	523	Me	sec-Bu
500	H	t-Bu	524	Me	t-Bu
501	H	-COOH	525	Me	-COOH
502	H	-COOMe	526	Me	-COOMe
503	H	$-CONH_2$	527	Me	$-CONH_2$
504	H	-CONHMe	528	Me	-CONHMe
505	H	-CN	529	Me	-CN
506	H	$-CH_2OH$	530	Me	$-CH_2OH$
507	H	$-CH_2OMe$	531	Me	$-CH_2OMe$
508	H	$-CH_2COOH$	532	Me	$-CH_2COOH$
509	H	$-CH_2COOMe$	533	Me	$-CH_2COOMe$
510	H	$-CH_2COPh$	534	Me	$-CH_2COPh$
511	H	$-CH_2CONH_2$	535	Me	$-CH_2CONH_2$
512	H	$-CH_2CN$	536	Me	$-CH_2CN$
513	H	$-CH_2CHO$	537	Me	$-CH_2CHO$
514	H	$-CH_2CF_3$	538	Me	$-CH_2CF_3$
515	H	$-CH_2SH$	539	Me	$-CH_2SH$

Table 34



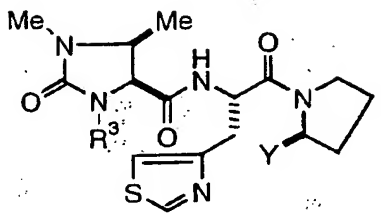
Example No.	R^3	Y	Example No.	R^3	Y
540	H	Me	564	Me	Me
541	H	Et	565	Me	Et
542	H	n-Pr	566	Me	n-Pr
543	H	i-Pr	567	Me	i-Pr
544	H	c-Pr	568	Me	c-Pr
545	H	n-Bu	569	Me	n-Bu
546	H	i-Bu	570	Me	i-Bu
547	H	sec-Bu	571	Me	sec-Bu
548	H	t-Bu	572	Me	t-Bu
549	H	-COOH	573	Me	-COOH
550	H	-COOMe	574	Me	-COOMe
551	H	$-CONH_2$	575	Me	$-CONH_2$
552	H	-CONHMe	576	Me	-CONHMe
553	H	-CN	577	Me	-CN
554	H	$-CH_2OH$	578	Me	$-CH_2OH$
555	H	$-CH_2OMe$	579	Me	$-CH_2OMe$
556	H	$-CH_2COOH$	580	Me	$-CH_2COOH$
557	H	$-CH_2COOMe$	581	Me	$-CH_2COOMe$
558	H	$-CH_2COPh$	582	Me	$-CH_2COPh$
559	H	$-CH_2CONH_2$	583	Me	$-CH_2CONH_2$
560	H	$-CH_2CN$	584	Me	$-CH_2CN$
561	H	$-CH_2CHO$	585	Me	$-CH_2CHO$
562	H	$-CH_2CF_3$	586	Me	$-CH_2CF_3$
563	H	$-CH_2SH$	587	Me	$-CH_2SH$

Table 35



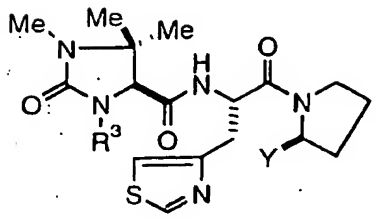
Example No.	R^3	Y	Example No.	R^3	Y
588	H	Me	612	Me	Me
589	H	Et	613	Me	Et
590	H	n-Pr	614	Me	n-Pr
591	H	i-Pr	615	Me	i-Pr
592	H	c-Pr	616	Me	c-Pr
593	H	n-Bu	617	Me	n-Bu
594	H	i-Bu	618	Me	i-Bu
595	H	sec-Bu	619	Me	sec-Bu
596	H	t-Bu	620	Me	t-Bu
597	H	-COOH	621	Me	-COOH
598	H	-COOMe	622	Me	-COOMe
599	H	$-CONH_2$	623	Me	$-CONH_2$
600	H	-CONHMe	624	Me	-CONHMe
601	H	-CN	625	Me	-CN
602	H	$-CH_2OH$	626	Me	$-CH_2OH$
603	H	$-CH_2OMe$	627	Me	$-CH_2OMe$
604	H	$-CH_2COOH$	628	Me	$-CH_2COOH$
605	H	$-CH_2COOMe$	629	Me	$-CH_2COOMe$
606	H	$-CH_2COPh$	630	Me	$-CH_2COPh$
607	H	$-CH_2CONH_2$	631	Me	$-CH_2CONH_2$
608	H	$-CH_2CN$	632	Me	$-CH_2CN$
609	H	$-CH_2CHO$	633	Me	$-CH_2CHO$
610	H	$-CH_2CF_3$	634	Me	$-CH_2CF_3$
611	H	$-CH_2SH$	635	Me	$-CH_2SH$

Table 36



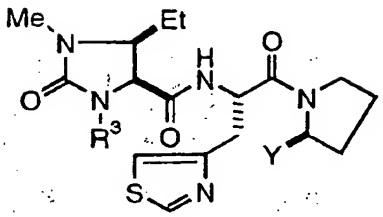
Example No.	R^3	Y	Example No.	R^3	Y
636	H	Me	661	Me	Me
637	H	Et	662	Me	Et
638	H	n-Pr	663	Me	n-Pr
639	H	i-Pr	664	Me	i-Pr
640	H	c-Pr	665	Me	c-Pr
641	H	n-Bu	666	Me	n-Bu
642	H	i-Bu	667	Me	i-Bu
643	H	sec-Bu	668	Me	sec-Bu
645	H	t-Bu	669	Me	t-Bu
646	H	-COOH	670	Me	-COOH
647	H	-COOMe	671	Me	-COOMe
648	H	$-CONH_2$	672	Me	$-CONH_2$
649	H	-CONHMe	673	Me	-CONHMe
650	H	-CN	674	Me	-CN
651	H	$-CH_2OH$	675	Me	$-CH_2OH$
652	H	$-CH_2OMe$	676	Me	$-CH_2OMe$
653	H	$-CH_2COOH$	677	Me	$-CH_2COOH$
654	H	$-CH_2COOMe$	678	Me	$-CH_2COOMe$
655	H	$-CH_2COPh$	679	Me	$-CH_2COPh$
656	H	$-CH_2CONH_2$	680	Me	$-CH_2CONH_2$
657	H	$-CH_2CN$	681	Me	$-CH_2CN$
658	H	$-CH_2CHO$	682	Me	$-CH_2CHO$
659	H	$-CH_2CF_3$	683	Me	$-CH_2CF_3$
660	H	$-CH_2SH$	684	Me	$-CH_2SH$

Table 37



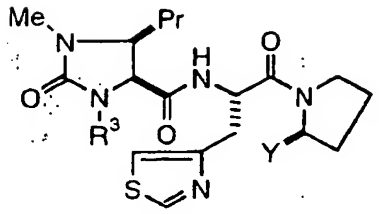
Example No.	R^3	Y	Example No.	R^3	Y
685	H	Me	709	Me	Me
686	H	Et	710	Me	Et
687	H	n-Pr	711	Me	n-Pr
688	H	i-Pr	712	Me	i-Pr
689	H	c-Pr	713	Me	c-Pr
690	H	n-Bu	714	Me	n-Bu
691	H	i-Bu	715	Me	i-Bu
692	H	sec-Bu	716	Me	sec-Bu
693	H	t-Bu	717	Me	t-Bu
694	H	-COOH	718	Me	-COOH
695	H	-COOMe	719	Me	-COOMe
696	H	$-CONH_2$	720	Me	$-CONH_2$
697	H	-CONHMe	721	Me	-CONHMe
698	H	-CN	722	Me	-CN
699	H	$-CH_2OH$	723	Me	$-CH_2OH$
700	H	$-CH_2OMe$	724	Me	$-CH_2OMe$
701	H	$-CH_2COOH$	725	Me	$-CH_2COOH$
702	H	$-CH_2COOMe$	726	Me	$-CH_2COOMe$
703	H	$-CH_2COPh$	727	Me	$-CH_2COPh$
704	H	$-CH_2CONH_2$	728	Me	$-CH_2CONH_2$
705	H	$-CH_2CN$	729	Me	$-CH_2CN$
706	H	$-CH_2CHO$	730	Me	$-CH_2CHO$
707	H	$-CH_2CF_3$	731	Me	$-CH_2CF_3$
708	H	$-CH_2SH$	732	Me	$-CH_2SH$

Table 38



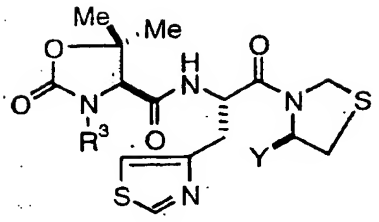
Example No.	R^3	Y	Example No.	R^3	Y
733	H	Me	757	Me	Me
734	H	Et	758	Me	Et
735	H	n-Pr	759	Me	n-Pr
736	H	i-Pr	760	Me	i-Pr
737	H	c-Pr	761	Me	c-Pr
738	H	n-Bu	762	Me	n-Bu
739	H	i-Bu	763	Me	i-Bu
740	H	sec-Bu	764	Me	sec-Bu
741	H	t-Bu	765	Me	t-Bu
742	H	-COOH	766	Me	-COOH
743	H	-COOMe	767	Me	-COOMe
744	H	$-CONH_2$	768	Me	$-CONH_2$
745	H	-CONHMe	769	Me	-CONHMe
746	H	-CN	770	Me	-CN
747	H	$-CH_2OH$	771	Me	$-CH_2OH$
748	H	$-CH_2OMe$	772	Me	$-CH_2OMe$
749	H	$-CH_2COOH$	773	Me	$-CH_2COOH$
750	H	$-CH_2COOMe$	774	Me	$-CH_2COOMe$
751	H	$-CH_2COPh$	775	Me	$-CH_2COPh$
752	H	$-CH_2CONH_2$	776	Me	$-CH_2CONH_2$
753	H	$-CH_2CN$	777	Me	$-CH_2CN$
754	H	$-CH_2CHO$	778	Me	$-CH_2CHO$
755	H	$-CH_2CF_3$	779	Me	$-CH_2CF_3$
756	H	$-CH_2SH$	780	Me	$-CH_2SH$

Table 39



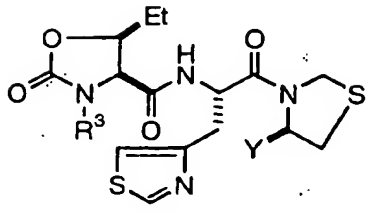
Example No.	R^3	Y	Example No.	R^3	Y
781	H	Me	805	Me	Me
782	H	Et	806	Me	Et
783	H	n-Pr	807	Me	n-Pr
784	H	i-Pr	808	Me	i-Pr
785	H	c-Pr	809	Me	c-Pr
786	H	n-Bu	810	Me	n-Bu
787	H	i-Bu	811	Me	i-Bu
788	H	sec-Bu	812	Me	sec-Bu
789	H	t-Bu	813	Me	t-Bu
790	H	-COOH	814	Me	-COOH
791	H	-COOMe	815	Me	-COOMe
792	H	$-CONH_2$	816	Me	$-CONH_2$
793	H	-CONHMe	817	Me	-CONHMe
794	H	-CN	818	Me	-CN
795	H	$-CH_2OH$	819	Me	$-CH_2OH$
796	H	$-CH_2OMe$	820	Me	$-CH_2OMe$
797	H	$-CH_2COOH$	821	Me	$-CH_2COOH$
798	H	$-CH_2COOMe$	822	Me	$-CH_2COOMe$
799	H	$-CH_2COPh$	823	Me	$-CH_2COPh$
800	H	$-CH_2CONH_2$	824	Me	$-CH_2CONH_2$
801	H	$-CH_2CN$	825	Me	$-CH_2CN$
802	H	$-CH_2CHO$	826	Me	$-CH_2CHO$
803	H	$-CH_2CF_3$	827	Me	$-CH_2CF_3$
804	H	$-CH_2SH$	828	Me	$-CH_2SH$

Table 40



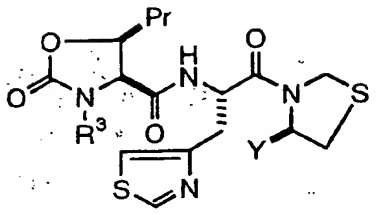
Example No.	R^3	Y	Example No.	R^3	Y
829	H	Me	853	Me	Me
830	H	Et	854	Me	Et
831	H	n-Pr	855	Me	n-Pr
832	H	i-Pr	856	Me	i-Pr
833	H	c-Pr	857	Me	c-Pr
834	H	n-Bu	858	Me	n-Bu
835	H	i-Bu	859	Me	i-Bu
836	H	sec-Bu	860	Me	sec-Bu
837	H	t-Bu	861	Me	t-Bu
838	H	-COOH	862	Me	-COOH
839	H	-COOMe	863	Me	-COOMe
840	H	$-CONH_2$	864	Me	$-CONH_2$
841	H	-CONHMe	865	Me	-CONHMe
842	H	-CN	866	Me	-CN
843	H	$-CH_2OH$	867	Me	$-CH_2OH$
844	H	$-CH_2OMe$	868	Me	$-CH_2OMe$
845	H	$-CH_2COOH$	869	Me	$-CH_2COOH$
846	H	$-CH_2COOMe$	870	Me	$-CH_2COOMe$
847	H	$-CH_2COPh$	871	Me	$-CH_2COPh$
848	H	$-CH_2CONH_2$	872	Me	$-CH_2CONH_2$
849	H	$-CH_2CN$	873	Me	$-CH_2CN$
850	H	$-CH_2CHO$	874	Me	$-CH_2CHO$
851	H	$-CH_2CF_3$	875	Me	$-CH_2CF_3$
852	H	$-CH_2SH$	876	Me	$-CH_2SH$

Table 41



Example No.	R^3	Y	Example No.	R^3	Y
877	H	Me	901	Me	Me
878	H	Et	902	Me	Et
879	H	n-Pr	903	Me	n-Pr
880	H	i-Pr	904	Me	i-Pr
881	H	c-Pr	905	Me	c-Pr
882	H	n-Bu	906	Me	n-Bu
883	H	i-Bu	907	Me	i-Bu
884	H	sec-Bu	908	Me	sec-Bu
885	H	t-Bu	909	Me	t-Bu
886	H	-COOH	910	Me	-COOH
887	H	-COOMe	911	Me	-COOMe
888	H	$-CONH_2$	912	Me	$-CONH_2$
889	H	-CONHMe	913	Me	-CONHMe
890	H	-CN	914	Me	-CN
891	H	$-CH_2OH$	915	Me	$-CH_2OH$
892	H	$-CH_2OMe$	916	Me	$-CH_2OMe$
893	H	$-CH_2COOH$	917	Me	$-CH_2COOH$
894	H	$-CH_2COOMe$	918	Me	$-CH_2COOMe$
895	H	$-CH_2COPh$	919	Me	$-CH_2COPh$
896	H	$-CH_2CONH_2$	920	Me	$-CH_2CONH_2$
897	H	$-CH_2CN$	921	Me	$-CH_2CN$
898	H	$-CH_2CHO$	922	Me	$-CH_2CHO$
899	H	$-CH_2CF_3$	923	Me	$-CH_2CF_3$
900	H	$-CH_2SH$	924	Me	$-CH_2SH$

Table 42



Example No.	R^3	Y	Example No.	R^3	Y
925	H	Me	949	Me	Me
926	H	Et	950	Me	Et
927	H	n-Pr	951	Me	n-Pr
928	H	i-Pr	952	Me	i-Pr
929	H	c-Pr	953	Me	c-Pr
930	H	n-Bu	954	Me	n-Bu
931	H	i-Bu	955	Me	i-Bu
932	H	sec-Bu	956	Me	sec-Bu
933	H	t-Bu	957	Me	t-Bu
934	H	-COOH	958	Me	-COOH
935	H	-COOMe	959	Me	-COOMe
936	H	$-CONH_2$	960	Me	$-CONH_2$
937	H	-CONHMe	961	Me	-CONHMe
938	H	-CN	962	Me	-CN
939	H	$-CH_2OH$	963	Me	$-CH_2OH$
940	H	$-CH_2OMe$	964	Me	$-CH_2OMe$
941	H	$-CH_2COOH$	965	Me	$-CH_2COOH$
942	H	$-CH_2COOMe$	966	Me	$-CH_2COOMe$
943	H	$-CH_2COPh$	967	Me	$-CH_2COPh$
944	H	$-CH_2CONH_2$	968	Me	$-CH_2CONH_2$
945	H	$-CH_2CN$	969	Me	$-CH_2CN$
946	H	$-CH_2CHO$	970	Me	$-CH_2CHO$
947	H	$-CH_2CF_3$	971	Me	$-CH_2CF_3$
948	H	$-CH_2SH$	972	Me	$-CH_2SH$

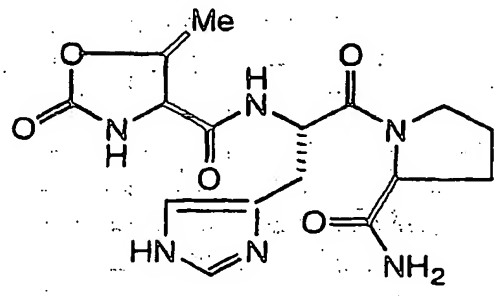
Referential example

Preparation of cis-L-5-methyl-2-oxo-oxazolidine-4-carbonyl-L-hystidyl-L-prolineamide (52)

[0120] In a manner similar to that described in the method of Example 1 - 3, N-hydroxysuccinimide-ester of cis-L-5-methyl-2-oxo-oxazolidine-4-carboxylic acid which was synthesized by reacting cis-L-5-methyl-2-oxo-oxazolidine-4-carboxylic acid (226 mg, 1.56 mmol), N-hydroxysuccinimide (179 mg, 1.56 mmol), and DCC (338 mg, 1.63 mmol) in N, N-dimethylformamide (5 ml) was condensed with L-hystidyl-L-prolineamide hydrobromide (870 mg, 1.56 mmol), which was synthesized in accordance with the method described in Bull. Chem. Soc. Jpn, 44, 1689 (1971), in the presence of triethylamine (0.87 ml, 6.24 mmol) to give the referential compound (42) (223 mg, 38%). The chemical formula was shown below.

$[\alpha]_D$ = - 49.9° (c=0.505, MeOH, 24°C).
NMR(CD_3OD) : 7.60 (1H, s), 6.97 (1H, s), 4.90 (2H, m), 4.41 (1H, dd, J=3.3, 8.5 Hz), 4.35 (1H, d, J=8.4 Hz), 3.85 (1H, m), 3.43 (1H, m), 3.13 (1H, dd, J=6.6, 14.7 Hz), 2.98 (1H, m), 2.29 (1H, m), 2.00 (3H, m), 1.22 and 1.29 (total 3H, d, J=6.3 Hz).
Elemental analysis ($C_{16}H_{22}N_6O_5$ $2H_2O$)

Calcd. :	C,46.37;	H,6.32;	N,20.28.
Found :	C,46.30;	H,6.27;	N,20.54.



Test example 1

Anti-recerpine action after oral administration of test compounds

[0121] Reserpine-induced hypothemia mice (ddY, male, body weight: 30 to 40 g) were prepared by the subcutaneous administration of reserpine in back side of the rat (3 mg/kg) at 18 hours before test compounds administration. Mice with their body temperature about 25 °C were used in the experiment. Test compounds were solubilized in saline and 0.2 ml (10 μmol/kg) of them were administered by sonde for oral administration. After the administration, rectal temperature was measured at 30, 60, 120, 180, 240, 300, and 360 min. The area under curve (AUC) of the body temperature-time profile was calculated by the general trapezoidal method. In the control experiment, vehicle (saline) was administered to mice and the rectal temperature was measured by the same protocol. The effective dose, which can increase the average of body temperature at 1 °C for 420 min in reserpine-induced hypothermia mice after oral administration of the test compounds, is calculated by the following equation:

$$\text{Effective dose} = \frac{\text{Orally administered dose}}{\text{AUC(test compounds)-AUC(vehicle)/420}}$$

Effective dose: Dose which can increase the average of body temperatures at 1 °C for 420 min in reserpine-induced hypothermia mice.

AUC (test compounds): The area under curve (AUC) of the body temperature-time profile for 420 min after oral administration of test compounds was calculated by the general trapezoidal method.

AUC (vehicle): The area under curve (AUC) of the body temperature-time profile for 420 min after oral administration of saline was calculated by the general trapezoidal method.

[0122] The results were shown in Table 43.

Table 43

	Dose which can increase the average of body temperatures at 1 °C for 420 min in reserpine-induced hypothermia mice (by oral) (μmol/kg)
TRH	42.68
I-4	0.86
I-5	1.22
I-10	1.14
I-11	2.03
I-30	2.59
I-40	1.65

Test example 2

Anti recerpine action after intravenous and intracerebroventicular administration of test compounds

[0123] Recerpine-induced hypothermia mice (ddY, male) were prepared by the administration of reserpine (3 mg/kg) at 18 hours before test compounds administration. Mice with their body temperature about 25 °C were used in the experiment. Test compounds were solubilized in saline and 0.1 ml (1 μmol/kg) of them were administered intravenously and 0.005 ml (0.21 μmol/kg) of them were administered intracerebroventicularly, respectively. After the administration, rectal temperature was measured at 30, 60, 120, and 180 min. The area under curve (AUC) of the body temperature-time profile was calculated by the general trapezoidal method. In the control experiment, vehicle (saline) was administered to mice intravenously or intracerebroventicularly and the rectal temperature was measured by the same protocol. The effective dose, which can increase the average of body temperatures at 1 °C for 180 min in reserpine-induced hypothermia mice after intravenous or intracerebroventicular administration of the test compounds, is calculated by the following equation:

$$\text{Effective dose} = \frac{\text{Orally administered dose}}{\text{AUC(test compounds)-AUC(vehicle)}}$$

$$\text{Effective dose} = \frac{\text{Orally administered dose}}{\text{AUC(test compounds)-AUC(vehicle)/180}}$$

Effective dose: Dose which can increase the average of body temperatures at 1 °C for 180 min in reserpine-induced hypothermia mice.

AUC (test compounds): The area under curve (AUC) of the body temperature-time profile for 180 min after intravenous or intracerebroventicular administration of test compounds was calculated by the general trapezoidal method.

AUC (vehicle): The area under curve (AUC) of the body temperature-time profile for 180 min after intravenous or intracerebroventicular administration of saline was calculated by the general trapezoidal method.

[0124] The results were shown in Table 44.

Table 44

	Dose which can increase the average of body temperatures at 1 °C for 180 min in reserpine-induced hypothermia mice (μmol/kg)	
	administered intracerebroventicularly	administered intravenously
TRH	0.033	9.84
I-10	0.025	0.11

Test example 3

Effect on acetylcholine release

[0125] Male Wister rats (body weight: 250 to 300 g) which were fasted over night and anesthetized with uretane were placed in stereotaxic frame for rats. After the skin of scalp was incised and the skull was exposed, the cortex of frontal lobe was drilled (A 3.7, L 3.0, H 4.0). The dialysis probe used in the present experiment was I-shaped with a 3 mm long polycarbonate membrane tubing (CMA-12, BAS Co., LTD). Body temperature of rats, were kept at 37 °C by a hot blanket. Perfusion was performed at a constant rate of 2 μl/min with Ringer's solution containing 10 μM physostigmine. Perfusate were collected every 30 min. After the perfusion for 2 hours, test compounds (24 μmol/kg) solubilized in saline were administered orally to rats and then perfusion was continued for 6 hours. The concentrations of acetylcholine in perfusate were determined by a HPLC/ECD. The acetylcholine level before the administration of test compound was defined as the average baseline level (100 %). Data represent the increase of acetylcholine content of each fraction, expressed as a percentage compared to the average baseline level. The result was shown in Figure 1.

Test example 4

The change of blood glucose levels after the duodenal administration of the test compounds to rats

[0126] Fasted male Wistar rats (250-350 g) were anesthetized with urethane. Test compounds were solubilized in saline and administered intravenously (50 μmol/kg). Body temperature of rats were kept at 37 °C by a hot blanket. After the administration, blood was collected from jugular vein at 5, 15, 30, 60, 120, 180, 240, 300, 360, 420, and 480 min and blood glucose levels were measured (BM Test blood sugar, Wako Chemical Indus.). The blood glucose levels at each sampling time in vehicle (saline)-treated rats were defined as the baseline level (100 %). Data represent the changes of blood glucose levels after the duodenal administration of test compounds to rats, expressed as a percentage compared to the baseline level. The results was shown in Figure 2. The date was shown in Table 45.

Table 45

Time (min)	TRH	Compound (I-10)
0	116.3	107.7
5	114.6	119.9
15	123.3	104.3
30	137.9	109.1
60	153.5	112.1
120	139.1	126.5
180	119.1	105.3
240	112.6	110.9
300	113.2	104.0
360	103.5	100.4

Table 45 (continued)

Time (min)	TRH	Compound (I-10)
420	102.6	102.6
480	97.1	111.8

Formulation example

Formulation example 1

[0127] Granules are prepared using the following ingredients.

Ingredients		
	The compound represented by the formula (I)	10 mg
	Lactose	700 mg
	Corn starch	274 mg
	HPC-L	16 mg
		1000 mg

[0128] The compound represented by the formula (I) and lactose were made pass through a 60 mesh sieve. Corn starch was made pass through a 120 mesh sieve. They were mixed by a twin shell blender. An aqueous solution of HPC-L (low mucosity hydroxypropylcellulose) was added to the mixture and the resulting mixture was kneaded, granulated (by the extrusion with pore size 0.5 to 1 mm mesh), and dried. The dried granules thus obtained were sieved by a swing sieve (12/60 mesh) to yield the granules.

Formulation 2

[0129] Powders for filling capsules are prepared using the following ingredients.

Ingredients		
	The compound represented by the formula (I)	10 mg
	Lactose	79 mg
	Corn starch	10 mg
	Magnesium stearate	1 mg
		100 mg

[0130] The compound represented by the formula (I) and lactose were made pass through a 60 mesh sieve. Corn starch was made pass through a 120 mesh sieve. These ingredients and magnesium stearate were mixed by a twin shell blender. 100 mg of the 10-fold trituration was filled into a No. 5 hard gelatin capsule.

Formulation 3

[0131] Granules for filling capsules are prepared using the following ingredients.

Ingredients	The compound represented by the formula (I)	15 mg
	Lactose	90 mg
	Corn starch	42 mg
	HPC-L	3 mg
		150 mg

[0132] The compound represented by the formula (I) and lactose were made pass through a 60 mesh sieve. Corn starch was made pass through a 120 mesh sieve. After mixing them, an aqueous solution of HPC-L was added to the mixture and the resulting mixture was kneaded, granulated, and dried. After the dried granules were lubricated, 150 mg of that were filled into a No. 4 hard gelatin capsule.

Formulation 4

[0133] Tablets are prepared using the following ingredients.

Ingredients	The compound represented by the formula (I)	10 mg
	Lactose	90 mg
	Microcrystal cellulose	30 mg
	CMC-Na	15 mg
	Magnesium stearate	5 mg
		150 mg

[0134] The compound represented by the formula (I), lactose, microcrystal cellulose, and CMC-Na (carboxymethylcellulose sodium salt) were made pass through a 60 mesh sieve and then mixed. The resulting mixture was mixed with magnesium stearate to obtain the mixed powder for the tablet formulation. The mixed powder was compressed to yield tablets of 150 mg.

Formulation example 5

[0135] Sustained release tablets are prepared using the following ingredients.

Ingredients	The compound represented by the formula (I)	15 mg
	Lactose	20 mg
	Microcrystal cellulose	100 mg
	Magnesium stearate	5 mg
	Lovely wax-120 H	110 mg
		250 mg

[0136] The compound represented by the formula (I), lactose, and microcrystal cellulose were made pass through a 60 mesh sieve and were mixed. Mixpowders were heated and solubilized with lovely wax-120 H (Froint Inds.) and then granulated.. Magnesium stearate previously made pass through a 60 mesh sieve was added to the obtained granules and the resulting granules were compressed to yield sustained-release tablets.

Formulation example 6

Sustained release double layered tablet are prepared using the following ingredients.

[0137]

Ingredients Immediately release layer	
The compound represented by the formula (I)	15 mg
Lactose	25 mg
Microcrystal cellulose	100 mg
Methylcellulose	5 mg
Magnesium stearate	5 mg
	150 mg

Sustained layer	
The compound represented by the formula (I)	15 mg
Lactose	25 mg
Microcrystal cellulose	90 mg
Stearic acid	10 mg
Methylcellulose	5 mg
Magnesium stearate	5 mg
	150 mg

Immediately release layer : The compound represented by the formula (I), lactose, and microcrystal cellulose were made pass through a 60 mesh sieve and were mixed. A solution of methylcellulose was added to the mixture and the resulting mixture was kneaded, granulated, and dried to yield the granules. Sustained release layer : The compound represented by the formula (I), lactose, and microcrystal cellulose were made pass through a 60 mesh sieve and were mixed. Stearic acid was added to the mixture and the resulting mixture was heated and dissolved. They were kneaded, were granulated, and were dried to yield the granules. Double layered tablet formation : Magnesium stearate was added to the granules of immediately release layer and the resulting mixture was compressed. Subsequently, magnesium stearate was added to the granules of immediately release layer and the resulting mixture was compressed on to yield sustained release double layered tablets.

Formulation example 7

[0138] Enteric coated granules are prepared using the following ingredients.

Ingredients	The compound represented by the formula (I)	30 mg
	Microcrystal cellulose	125 mg
	Corn starch	50 mg
	CMC-Na	25 mg
	HPC or MC	10 mg
		240 mg

(Coating solution)	
HP-55	10.5 mg
Fatty acid ester of glycerin	2.0 mg
Ethanol	41.0 mg
Dichloromethane	46.5 mg
Talc	4 mg

[0139] The active ingredient, microcrystal cellulose, corn starch, and CMC-Na were made pass through a 20 mesh sieve and mixed thoroughly. A solution of HPC (hydroxypropylcellulose) or MC (methylcellulose) was added to the mixture and the kneading was made pass through a 16 mesh sieve. The obtained granules were dried at 50 to 60 °C. The dried granules were spray-coated with a solution of HP-55 (hydroxypropylmethylcellulose phthalate, Shinetsu Kagaku inc.) in fatty acid ester of glycerin, ethanol, dichloromethane, and talc to yield the enteric coated granules.

Formulation 8

[0140] Enteric coated granules are prepared using the following ingredients.

Ingredients	The compound represented by the formula (I)	30 mg
	Microcrystal cellulose	155 mg
	Corn starch	60 mg
	CMC-Na	25 mg
	HPC or MC	5 mg
		275 mg

(Coating solution)	
Eudragit L30D-55	46.8 mg
Polysolvate 80	0.7 mg

(continued)

(Coating solution)	
PEG 6000	1.4 mg
Talc	4.2 mg
Purified water	46.8 mg

[0141] The granules which are prepared in a manner similar to that described in the method of Formulation example 7 was coated with the coating solution comprising the solution of Eudragit L30D-55 (Röhm Pharma) in polysolvate 80 (polyoxyethylenesorbitan monooleate, Kao inc.), PEG 6000, talc, and purified water. After the obtained granules were dried, the resulting granules were made pass through a 16 mesh sieve to yield the enteric coated granules.

Formulation example 9

[0142] Sublingual tablets are prepared using the following ingredients.

Ingredients	The compound represented by the formula (I)	10 mg
	Lactose	70 mg
	Corn starch	12 mg
	Methylcellulose	5 mg
	Talc	2 mg
	Magnesium stearate	1 mg
		100 mg

[0143] The compound represented by the formula (I), lactose, and corn starch were made pass through a 80 mesh sieve and mixed. Mixpowder was kneaded with methylcellulose solution and granulated, dried, then the granules were lubricated.

Formulation example 10

[0144] Injections are prepared using the following ingredients.

Ingredients	The compound represented by the formula (I)	1 mg
	Glucose	2 mg
	Water for injection	997 mg
		1000 mg

[0145] The above ingredients were filled into ampoules.

Formulation 11

[0146] Freeze-dried injections are prepared using the following ingredients.

Ingredients	The compound represented by the formula (I)	1 mg
	D-mannitol	200 mg
	Water for injection	779 mg
		1000 mg

[0147] The above ingredients were filled into ampoules for freeze-drying and the ampoules were freeze-dried to yield the freeze-dried injections.

Formulation 12

[0148] Suppositories are prepared using the following ingredients.

Ingredients	The compound represented by the formula (I)	30 mg
	Witepsol	1470 mg
		1500 mg

[0149] The compound represented by the formula (I) was made pass through a 60 mesh sieve. The compound was dispersed in the solution of the melted witepsol (higher fatty acid triglyceride) at 50 to 60 °C. The solution was cooled to 38 to 40 °C with stirring to yield the medical fluid. The medical fluid was filled into a container of aluminum foil, sealed, and then cooled to yield the suppositories.

Formulation example 13

[0150] Nasals are prepared using the following ingredients.

Ingredients	The compound represented by the formula (I)	2 mg
	Carboxyvinylpolymer	5 mg
	L-Arginine	10 mg
	Sodium chloride	0.6 mg
	Purified water	84.2 mg
		100 mg

[0151] After the compound represented by the formula (I) was dissolved in carboxyvinylpolymer, L-arginine and sodium chloride was added to the solution. The solution's pH was adjusted and the mucosity was adjusted by adding purified water to yield the objective medical fluid.

Formation example 14

[0152] Endermatic formulation was prepared using the following ingredients:

Ingredients	The compound represented by the formula (I)	10 mg
	Iso-propyl myristate	990 mg
		1000 mg

[0153] After the compound represented by the formula (I) was dispersed in iso-propyl myristate, the mixture was mixed with acrylic adhesive formulation

(e.g. ニカゾール)

and was attached plastered to a support to yield endermatic formulation.

Formulation example 15

[0154] Ointment was prepared using the following ingredients.

Ingredients	The compound represented by the formula (I)	10 mg
	Liquid paraffin	7.5 mg
	Glycerol	82.5 mg
		100 mg

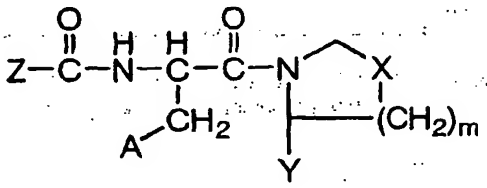
[0155] The compound represented by the formula (I) was dispersed in liquid paraffin and kneaded to yield the ointment.

Industrial Applicability

[0156] The novel peptide derivatives having 3-(4-thiazolyl or 5-thiazolyl)-alanine residue and having an effect of activating the central nervous system were provided.

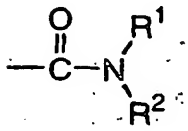
Claims

1. A peptide derivative of the formula (I):

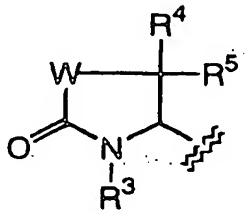


(I)

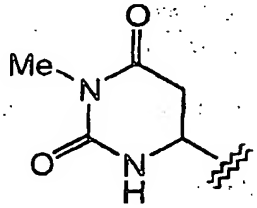
wherein A is 4-thiazolyl or 5-thiazolyl wherein the nitrogen in the thiazolyl ring may be quarternary nitrogen which is formed with optionally substituted alkyl or alkenyl, X is a bond oxygen, or sulfur, m is an integer of 0 to 4, Y is optionally substituted alkyl, optionally substituted carboxy, cyano, or the substituent represented by the formula:



wherein R^1 and R^2 are independently hydrogen or optionally substituted alkyl, or R^1 and R^2 taken together with may form a non-aromatic heterocyclic ring the adjacent nitrogen which may contain oxygen, nitrogen, or sulfur and may be substituted, Z is the substituent represented by the formula:

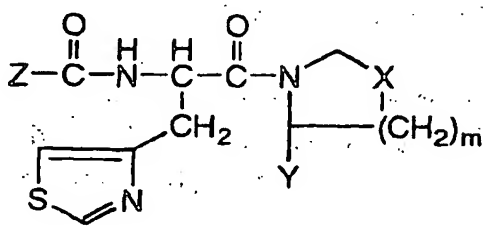


wherein R^3 is hydrogen, optionally substituted alkyl, optionally substituted carboxy, or optionally substituted acyl, R^4 and R^5 are each independently hydrogen or optionally substituted alkyl, and W is $-(CH_2)n-$ wherein n is 0, 1, 2, or 3, oxygen, sulfur, or optionally substituted imino, or the substituent represented by the formula:



its pharmaceutically acceptable salt, or hydrate thereof.

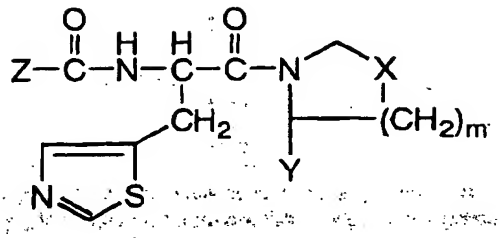
2. A peptide derivative of the formula (II):



(II)

wherein X, Y, Z, and m are as defined above, and the nitrogen in the thiazolyl ring may be quarternary nitrogen which is formed with optionally substituted alkyl or alkenyl, its pharmaceutically acceptable salt, or hydrate thereof.

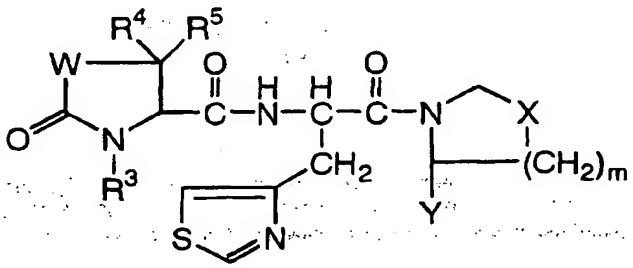
3. A peptide derivative of the formula (III):



(III)

wherein X, Y, Z, and m are as defined above, and the nitrogen in the thiazolyl ring may be quarternary nitrogen which is formed with optionally substituted alkyl or alkenyl, its pharmaceutically acceptable salt, or hydrate thereof.

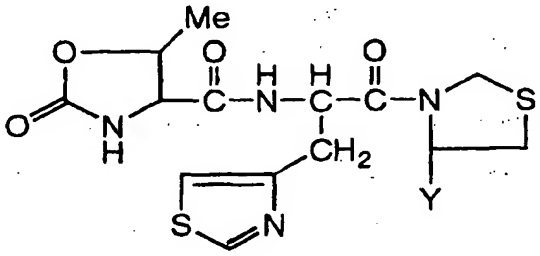
4. A peptide derivative of the formula (IV):



(IV)

wherein W, X, Y, m, R^3, R^4, and R^5 are as defined above, its pharmaceutically acceptable salt, or hydrate thereof.

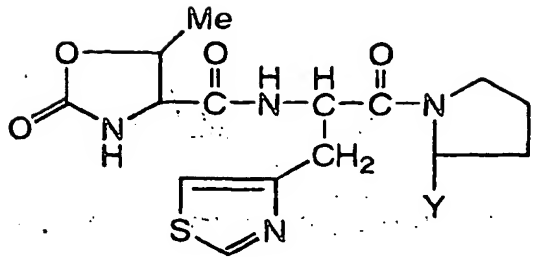
5. A peptide derivative of the formula (V):



(V)

wherein Y is as defined above, its pharmaceutically acceptable salt, or hydrate thereof.

6. A peptide derivative of the formula (VI):



(VI)

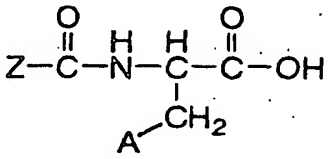
wherein Y is as defined above, its pharmaceutically acceptable salt, or hydrate thereof.

7. A peptide derivative of any one of claims 1 to 4 wherein m is 1 or 2, provided that X is not a bond when m is 1, its pharmaceutically acceptable salt, or hydrate thereof.

8. A peptide derivative of any one of claims 1 to 4 wherein m is 1 and Y is optionally substituted alkyl, optionally substituted carboxy, or optionally substituted carbamoyl, its pharmaceutically acceptable salt, or hydrate thereof.

9. A peptide derivative of any one of claims 1 to 4 wherein m is 2 or 3 and Y is optionally substituted alkyl, optionally substituted carboxy, or optionally substituted carbamoyl, its pharmaceutically acceptable salt, or hydrate thereof.

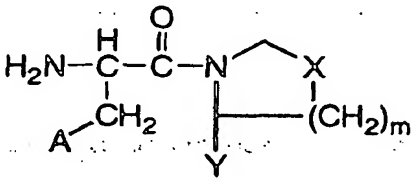
10. A compound represented by the formula (VII):



(VII)

wherein A and Z are as defined above.

11. A compound represented by the formula (VIII):



(VIII)

wherein A, X, Y, and m are as defined above.

12. A pharmaceutical composition which contains the compounds described in the claims 1 to 9 as an active ingredient.

13. A composition for activating the central nervous system which contains the compounds described in the claims 1 to 9 as an active ingredient.

14. A TRH derivative having such effect that the ratio represented by the blood glucose level of the active substance-administered group / the blood glucose level of the physiological saline-administered group is 0.7 to 1.3 in the rat

to which an effective amount of it for exhibiting the main activity is intravenously administered.

Figure 1

The effect of releasing acetylcholine in cerebral cortex when the test compound is orally administered to rats

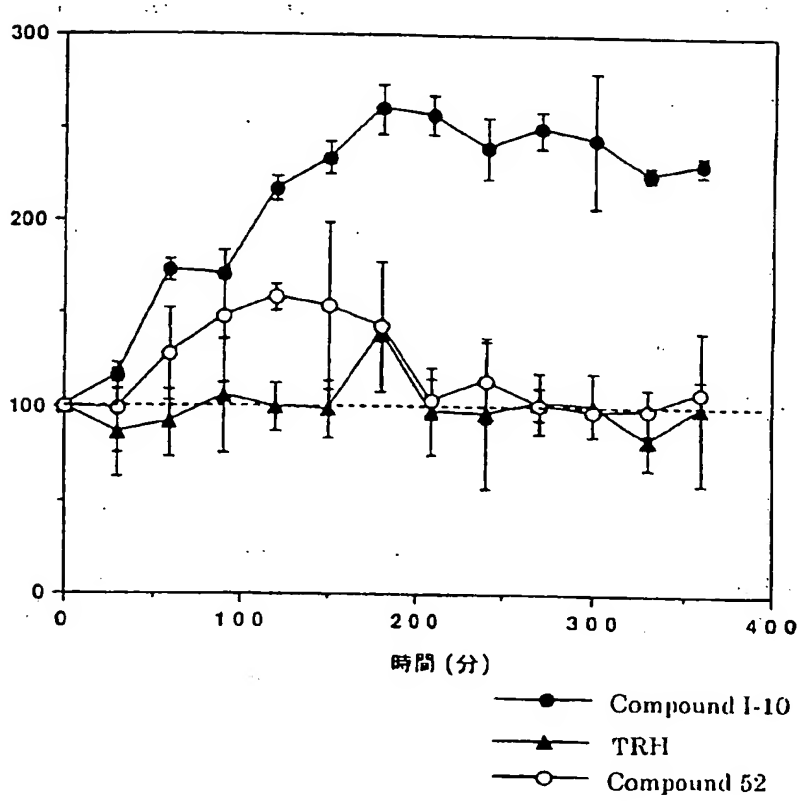
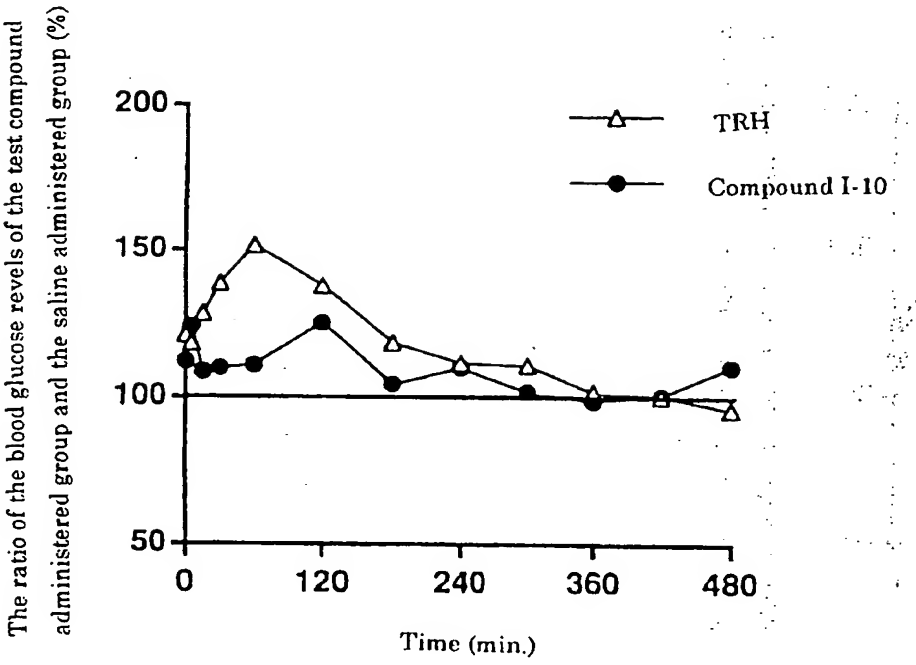


Figure 2

The transition of the blood glucose level by intravenous injection to rats



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02917

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 C07K5/078, 5/097, C07D417/06, 277/02, A61K38/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 C07K5/078, 5/097, C07D417/06, 277/02, A61K38/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA(STN), CAOLD(STN), REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, 3-236397, A (Japan Tobacco Inc.), October 22, 1991 (22. 10. 91) & EP, 384380, A1	1 - 13
A	JP, 52-3080, A (Chemie Gruenenthal GmbH.), January 11, 1977 (11. 01. 77) & DE, 2527723, A1 & US, 4045556, A & FR, 2287916, A1	1 - 13
A	JP, 52-116465, A (Takeda Chemical Industries, Ltd.), September 29, 1977 (29. 09. 77) & DE, 2712086, A1 & FR, 2345448, A1 & US, 4100152, A	1 - 13
A	JP, 62-234029, A (Tanabe Seiyaku Co., Ltd.), October 14, 1990 (14. 10. 90)(Family: none)	1 - 13
A	MIYAMOTO, M. et al., Effects of sustained release formulation of thyrotropin releasing hormone on behavioral abnormalities in	1 - 13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
November 4, 1997 (04. 11. 97)	November 11, 1997 (11. 11. 97)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02917

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	senescence-accelerated mice., Eur. J. Pharmacol. (1994) Vol. 271, p.357-p.366	
A	WO, 96/11209, A1 (Chiroscience Ltd.), April 18, 1996 (81. 04. 96) & EP, 784629, A1	1 - 11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02917

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1 to 13 relate to peptides represented by the formulae (I) to (VI), intermediates of the formulae (VII) and (VIII) for producing these peptides, and medicinal compositions and central nervous system activators containing these peptides as the active ingredients.

Claim 14 relates to TRH derivatives capable of giving a ratio of the blood sugar level of the test group to which the active compound is administered to that of the control group to which physiological saline is administered of from 0.7 to 1.3, after being intravenously injected into rats in such an effective dosage as to allow the exertion of the main effect.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02917

Continuation of Box No. II of continuation of first sheet (1)

It is considered that the special technical features of Claims 1 to 13 reside in the provision of the peptides represented by the formulae (I) to (VI) which are useful as medicinal compositions while the special technical feature of Claim 14 resides in the provision of the TRH derivatives which are capable of giving a blood sugar level ratio falling within a specific range and thus differ from the above-mentioned ones.

Such being the case, Claims 1 to 13 and Claim 14 do not have any technical feature in common. Therefore, it is obvious that this international application does not comply with the requirement of unity of invention.

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